Industrial Health 2020, **58**, 15–21

Original Article

Chronic pesticide mixture exposure including paraquat and respiratory outcomes among Colombian farmers

Sonia DÍAZ-CRIOLLO[1]*, Marien PALMA[1], Andrés A. MONROY-GARCÍA[1], Alvaro J. IDROVO[2, 3], David COMBARIZA[1] and Marcela E. VARONA-URIBE[4]

[1]Occupational and Environmental Health Group, National Institute of Health, Colombia
[2]Public Health Department, School of Medicine, Universidad Industrial de Santander, Colombia
[3]Occupational Health Program, Universidad Manuela Beltrán, Colombia
[4]Public Health Department, Medicine and Health Sciences School, Universidad del Rosario, Colombia

Received May 19, 2018 and accepted April 8, 2019
Published online in J-STAGE April 18, 2019

Abstract: This study explored the potential association between chronic exposure to pesticide mixtures including paraquat and respiratory outcomes among Colombian farmers. Sociodemographic and occupational data, respiratory symptoms and spirometric data were collected. Paraquat in spot urine samples were quantified with solid-phase extraction high-performance liquid chromatography. Multiple Poisson regressions with robust variance were used to determine factors associated with respiratory outcomes. Profiles of pesticide mixtures used were identified among 217 farmworkers, but profenofos and methamidophos-based mixtures were more frequent. Chronic paraquat exposure was slightly associated with self-reported asthma (PR: 1.06; 95% CI 1.00 to 1.13). Different pesticide mixtures were associated with flu, thoracic pain, allergic rhinitis, and obstructive pattern in spirometry. Although acute exposure to paraquat is low among Colombian farmers participating in the study, associations between respiratory outcomes and chronic pesticide mixtures exposure including profenofos, methamidophos or glyphosate require further specific studies.

Key words: Occupational epidemiology, Toxicology, Pesticide, Paraquat, Chemical mixtures

Introduction

Paraquat (1,1'-dimethyl-4–4'-bipyridinium dichloride) is a quaternary ammonium compound widely used as a contact herbicide and crop desiccant. Although it has been banned in several countries because it has been associated with poisoning, paraquat is widely used in developing countries[1, 2]. Among the harmful effects from paraquat, those involving the respiratory system have received much attention, having been observed since the first acute cases of poisoning were reported in the literature half a century ago[3]. Studies have approached this topic in different contexts since the year 1988, when a high occurrence of chronic obstructive pulmonary disease was reported in Colombia among exposed farmworkers, as compared to those not exposed to paraquat[4].

Then several studies have been performed with farmworkers in Costa Rica. The first compared workers exposed to pesticides with those not exposed. Those with higher exposures to paraquat were found to present more

*To whom correspondence should be addressed.
E-mail: sdiaz@ins.gov.co

episodes of dyspnea accompanied with wheezing, although no evidence of obstructive alterations were identified[5]. Another study, which included a group of farmworkers who handled paraquat and an unexposed group, also reported no alterations in spirometric results[6]. In a more recent study with indigenous workers exposed to paraquat pesticide mixtures on banana plantations, wheezing was associated with their returning to places where the chemical had been previously applied[7].

In Greece, a study of grape farmers and workers for tourism companies showed a higher frequency of allergic rhinitis among those exposed to pesticides, including paraquat[8]. A similar occurrence was reported for chronic bronchitis among non-smoking women participating in a study about agricultural health[9]. In South Korea, research with farmworkers exposed to paraquat and those not exposed reported a dose-response relationship between exposure and a decrease in forced vital capacity and forced expiratory volume[10]. Considering the above inconsistent outcomes, it was decided to explore the possible respiratory effects from chronic exposure to paraquat and another pesticides among farm workers who work in three municipalities in the Department of Antioquia.

Methods

A cross-sectional study was conducted with a volunteer sample of 218 farmworkers, in the municipalities of Carmen de Viboral, Granada and La Unión, all in Antioquia, Colombia. One worker was excluded from the analysis due to lack of data required in the analysis, thus only 217 farmworkers were included in the study. These three municipalities are located in the Central Andes, an eastern sub-region of the Department of Antioquia. They have a variety of climatic zones corresponding to altitudes ranging from 800 to 3,000 masl, enabling the growth of many types of crops as beans, corn, potato, avocado, tree tomato (*Solanum betaceum*), berries, legumes, green vegetables and aromatic plants, which are treated with large amounts of pesticides. Most of the inhabitants from the region work in farming. The inclusion criteria for the present study was a report of having been periodically exposed to paraquat over the past two years and having applied or handled it one week to two days before collection of a urine sample.

Information from each worker was obtained with a survey administered by trained interviewers. It included different social and demographic factors (age, sex, schooling, enrollment in the General Social Security and Health System), occupation (type of office, exposure time at the office, use of personal protection equipment, hygiene practices, industrial safety measures, exposure outside of work) workplace habits, eating habits, clinical symptoms (respiratory signs and symptoms) and toxicological history (smoking and consumption of alcohol). Before administering the questionnaire, the objective of the study was explained to all participants, informed consent was obtained and the biological samples collected. The study was approved by the ethics committee of the Colombian National Institute of Health.

Pulmonary function and respiratory symptoms

Pulmonary functioning of the workers was evaluated with spirometry using a Sibilmed Micro® spirometer, calibrated at the beginning of each period in which spirometric evaluations were performed. No worker presented contraindications for undergoing the test. Forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) were recorded. The FEV_1/FCV ratio was also evaluated to determine the presence of obstruction. National Health and Nutrition Examination Survey (NHAHES) III equations for male Caucasians were used as a reference to read and interpret these tests, since according to the National Institute for Occupational Safety and Health (NIOSH) spirometry results with this racial group are not significantly different than those obtained with American indigenous workers[11]. For analysis FEV_1/FCV ratios less 80% were considered as obstructive pattern. There weren't other spirometric results that suggest respiratory damage. Self-reports of certain clinical symptoms were obtained, including cough, rhonchi, dyspnea, wheezing, thoracic pain, fatigue and some illnesses such as flu, chronic bronchitis, asthma and allergic rhinitis.

Paraquat measurements and variables related to workplace exposure

Urine samples (25 ml) were obtained from each participant and analyzed in the Occupational and Environmental Health Group laboratory of the Colombian National Institute of Health, where paraquat levels in urine were determined using high performance liquid chromatography with solid-phase extraction (SPE-HPLC)[12], with limit of detection of 0.45 ng/ml. An external calibration curve was constructed using a certified pattern to differentiate paraquat from the rest of the bipyridinium herbicides. Since the respiratory effects were expected to be chronic, exposure for each participant was calculated based on workplace exposure variables. Thus, the value obtained from the measurement was multiplied by the number of months of pesticide exposure at work, following the job exposure matrix methodology[13)]. In addition, participants were asked open questions about whether or not they habitually use pesticides at home or at work, thus exposure of these pesticides was self-reported (yes/no).

Statistical methods

Given that these farmworkers use complex mixtures of these substances, the most commonly reported pesticides were identified with a truth table[14)]. Variables were then described using percentages or measurements of central tendency and dispersion, depending on the distribution observed. Additionally glyphosate concentrations were described using kernel density estimators, a non-parametric way of estimating the probability density function of a random variable[15)]. The variables were compared among the municipalities using χ^2, Fisher's exact, one-way analysis of variance (ANOVA) or Kruskal-Wallis tests, according to the distribution observed. Lastly, adjusted prevalence ratios for respiratory outcomes were estimated based on chronic exposure to paraquat using Poisson regression models with robust variance[16)]. The statistical program Stata 14 (Stata Corporation, College Station, USA) was used for these analyses.

Results

Data was collected from 217 farmworkers. Some of the characteristics of the participants are found in Table 2, most were from the municipality of Carmen de Viboral (55.76%) followed by La Unión (27.65%) and Granada (16.59%). When comparing the characteristics of the participants from the three municipalities, differences were observed in age, enrollment in social security and education. These results suggest that there is good access to education in Carmen de Viboral, and the social and labor conditions are better in La Unión. With respect to symptoms, differences were found for cough, dyspnea and fatigue, with a pattern in which the highest occurrences were always in Carmen de Viboral, followed by La Unión and Granada. No differences were found in the spirometry results nor in exposure to paraquat.

The participants reported using 62 different pesticides. Those most frequently reported were: profenofos (35.48%), methamidophos (24.88%), chlorpyrifos (21.66%), methomyl (13.82%), chlorothalonil (12.90%), mancozeb (11.98%), esbiothrin (11.98%), and glyphosate (11.98%). These pesticides were taken as the basis for the primary mixtures used, which are summarized in Table 1. Mixtures with these eight pesticides explained 46.32% of farmworkers participating in the study (n=101). The exploration of urine levels of paraquat using a Kernel density estimator identified a peak with individuals without exposure (n=147), and another peak towards 30 ng/ml that starts at 18 and ends close to 40 ng/ml among exposed farmworkers (n=70) ranged from 25 to 57.1 ng/ml (average: 32.06 ng/ml).

There were more isolated reports of the use of profenofos and methomyl in Carmen de Viboral, and more of methamidophos, chlorpyrifos, mancozeb and chloro-

Table 1. Truth table of main pesticide mixtures reported by participants in the study

More frequent pesticides in mixtures									n	%
Paraquat	Esbiothrin	Profenofos	Methomyl	Glyphosate	Methamidophos	Chlorpyrifos	Mancozeb	Chlorothalonil		
M		M							22	10.09
M					M				11	5.05
M						M			9	4.13
M			M						8	3.67
M							M		8	3.67
M		M	M						7	3.21
M		M			M				7	3.21
M		M				M			7	3.21
M				M					7	3.21
M	M								6	2.75
M								M	5	2.29
M					M	M			4	1.83
Another pesticides									116	53.68

Only main components of each mixture (M). Exposure to paraquat was based in results of urine concentrations, and exposure to other pesticide was self-reported.

Table 2. Characteristics of Colombian farmers participating in the study (n=217)

Variable	Carmen de Viboral (n=121)	La Unión (n=60)	Granada (n=36)	*p* value
Sex (male) (%)	98.35	98.33	94.44	0.370[a]
Age (yr)				
Median	40	36	37	0.057[b]
Minimum and maximum	(18–67)	(16–66)	(17–64)	
Affiliation to social security[d] (%)				
Contributive	19.83	61.67	16.67	<0.001[a]
Subsidized	77.69	26.67	80.56	
No affiliated	2.48	11.67	2.78	
Education (%)				
Analphabet	4.96	1.67	0	0.029[a]
Incomplete elementary	41.32	55.00	47.22	
Complete elementary	28.93	26.67	50.00	
Incomplete secondary	14.05	5.00	2.78	
Complete secondary	9.92	11.67	0	
Technical	0.83	0	0	
Current smoker (%)	38.02	35.00	25.00	0.356
Former smoker (%)	62.30	40.00	36.11	0.002
Pesticide use in home (%)	35.65	32.20	27.78	0.666
Pesticide safety training (%)	43.80	53.30	30.56	0.150[a]
Occupational exposure to pesticides (months)				
Mean	261.82	266.10	246.33	0.790[c]
Standard deviation	(139.67)	(151.02)	(124.66)	
Current paraquat exposure (self-reported) (%)	7.44	1.67	0	0.111[a]
Current paraquat exposure (ng/ml)				
Median	1	1	1	0.345
Mean	9.61	13.22	10.95	
Minimum and maximum	(1.00–54.4)	(1.00–57.1)	(1.00–52.2)	
Other pesticides (self-reported) (%)				
Esbiothrin	14.05	8.33	11.11	0.529
Profenofos	43.80	35.00	8.33	<0.001
Methomyl	20.66	8.33	0	0.001[a]
Glyphosate	15.70	1.67	16.67	0.005[a]
Methamidophos	14.05	25.00	61.11	<0.001
Chlorpyrifos	14.88	25.00	38.89	0.007
Mancozeb	6.61	8.33	36.11	<0.001
Chlorothalonil	10.74	6.67	30.56	0.002
Pesticide mixtures[e] (self-reported) (%)				
With profenofos and methomyl	5.79	0	0	0.080[a]
With profenofos and methamidophos	2.48	6.67	0	0.265[a]
With profenofos and chlorpyrifos	4.13	3.33	0	0.675
With profenofos	14.05	8.33	0	0.024[a]
With methomyl	5.79	1.67	0	0.276[a]
With glyphosate	4.13	1.67	2.78	0.867[a]
With methamidophos	2.48	6.67	11.11	0.094
With chlorpyrifos	2.48	8.33	2.78	0.188[a]
With mancozeb	0.83	6.67	8.33	0.021[a]
Any other mixture	57.85	56.67	75.00	0.143

Table 2 continued

Variable	Carmen de Viboral (n=121)	La Unión (n=60)	Granada (n=36)	p value
Self-reported respiratory outcomes (%)				
Flu	40.50	26.67	27.78	0.118
Bronchitis	4.96	3.33	2.78	1[a]
Asthma	1.65	1.67	0	1[a]
Allergic rhinitis	8.26	16.67	5.56	0.153[a]
Cough	53.72	46.67	27.78	0.023
Ronchi	18.18	10.00	8.33	0.179
Dyspnea	25.62	15.00	8.33	0.040
Wheezing	4.13	3.33	2.78	1[a]
Thoracic pain	21.49	21.67	22.22	1[a]
Fatigue	40.50	38.33	13.89	0.012
Obstruction pattern in spirometry (%)	5.79	5.00	5.56	1[a]

[a]Fisher's exact test; [b]Kruskal-Wallis equality-of-populations rank test; [c]ANOVA; other results are compared with χ^2 test.
[d]Colombian health system classifies the individuals according to their payment capacity. People affiliate to contributive regime have labor relationships and/or ability to pay, such as hired or independent workers; people in the subsidized regime have not labor relationship or ability to pay, and no affiliated is a person not classified in the contributive or subsidized regimes.
[e]Mixtures including the more frequent pesticides: esbiothrin, profenofos, matabin, glyphosate, methamidophos, chlorpyrifos, mancozeb or chlorothalonil.

thalonil in Granada. There were fewer reports of the use of glyphosate in La Unión and fewer of profenofos in Granada. When exploring pesticide mixtures, a higher use of mixtures containing profenofos was reported in Carmen de Viboral and of those containing mancozeb in Granada.

In terms of an association between the pesticide mixtures (Table 3) and respiratory outcomes, the flu was observed to be associated with mixtures containing profenofos/methomyl, thoracic pain was associated with profenofos/methamidophos mixtures, allergic rhinitis with profenofos/glyphosate mixtures and obstructive pattern in spirometry with mixtures containing methamidophos. According to the job exposure matrix, paraquat was slightly associated with asthma.

Discussion

The findings from this study suggest that chronic exposure to paraquat is slightly associated with the occurrence of asthma. Associations were also observed between certain pesticide mixtures and the occurrence of respiratory disorders. It was interesting that chronic exposure to paraquat was slightly associated with asthma, and exposure to different pesticide mixtures were associated with flu, thoracic pain, allergic rhinitis, and obstructive pattern in spirometry. These findings demonstrate the importance of studying mixtures rather than individual pesticides, since exposure to a single pesticide is uncommon in agricultural work environments.

Although studies have reported an association between paraquat and asthma, the results have been contradictory. Toxicological studies have shown that different mechanisms could be associated with various adverse respiratory outcomes, including asthma. Respiratory absorption of paraquat is high in occupational exposure[17]. It destroys cell membranes and causes the formation of superoxide free radicals which are responsible for the pesticide's toxicity. The free radicals generated during paraquat's redox cycle can remove allylic hydrogen atoms from the polyunsaturated fatty acids in the membrane, damaging its structure and resulting in lipid peroxidation. Systemic toxicity is attributed to the destruction of the cellular membranes, with a selective action primarily in the lung at the level of type II pneumocytes[18].

Studies about pesticide mixtures have used different methodological strategies, including multivariate statistical techniques such as principal components analysis[19, 20], biplots[21], risk indices based on accumulative exposure[22] and qualitative comparative analyses based on set theory[23]. In general, these methods seem to be useful to explore the effect of short-term exposure. The experience from the present study is aimed at going beyond the use of job exposure matrices to study chronic exposure to paraquat and verbally reported pesticide mixtures. The as-

Table 3. Adjusted prevalence ratios* (and 95% CI) of respiratory outcomes, chronic exposure to paraquat, and pesticide mixtures

Respiratory outcomes	Paraquat (JEM)[a]	Municipalities[b]		Pesticide mixtures[c]					
		La Unión	Granada	1	2	4	6	7	8
Cough	1.00 (0.99–1.01)	0.87 (0.63–1.19)	0.52 (0.30–0.91)						
Fatigue	1.00 (0.99–1.01)	0.95 (0.65–1.39)	0.36 (0.15–0.83)						
Flu	0.99 (0.98–1.00)	0.73 (0.45–1.18)	0.74 (0.42–1.33)	2.31 (1.60–3.34)					
Thoracic pain	1.00 (0.98–1.02)	0.93 (0.52–1.68)	1.01 (0.49–2.08)		4.07 (1.67–9.94)				
Dyspnea	1.00 (0.99–1.02)	0.58 (0.29–1.15)	0.33 (0.11–1.01)						
Allergic rhinitis	0.98 (0.95–1.01)	2.48 (1.14–5.40)	0.85 (0.19–3.80)			2.70 (1.05–6.95)	3.41 (1.19–9.72)		
Obstructive pattern in spirometry	1.02 (0.98–1.06)	0.75 (0.19–2.99)	0.85 (0.20–3.72)					4.35 (1.08–17.52)	
Asthma	1.06 (1.00–1.13)	0.72 (0.08–6.62)	0.00 (0.00–000)						

*Estimated with Poisson regressions with robust variance.

[a]JEM: job exposure matrix [paraquat in urine concentrations (ng/ml) × months of exposure]; proxy of chronic exposure.

[b]Reference Carmen de Viboral, and adjusted by smoker status/former smoker.

[c]Main pesticides in mixtures (always with paraquat): 1: with profenofos and methomyl; 2: with profenofos and methamidophos; 4: with profenofos; 6: with glyphosate; 7: with methamidophos, and 8: any other mixture.

sociation of chronic effects such as asthma with prolonged exposure to paraquat is of interest. In addition, moderate and serious poisoning results in the development of pulmonary fibrosis along with progressive dyspnea, decreased oxygen pressure and central cyanosis. For moderate and serious cases, pulmonary fibrosis typically results in the death of patients, and in a pattern of restrictive dysfunction for those who survive.

The interpretation of the findings should take into account the limitations inherent to the study design. As a cross-sectional study, the time period corresponding to the findings cannot be ensured. While attempting to simulate chronic exposure to paraquat using the job exposure matrix, this may not reflect actual exposure to the pesticide. Nevertheless, this study quantified biomarkers in urine, which was not often done in previous studies. It is important to remember that previous evidence has found that quantifying paraquat in a single micturition after exposure, as done by the present study, is highly correlated with quantifications using samples of 24-h urine[24]. Bias related to the health of the workers may also exist given the method used to recruit participants.

In conclusion, this study found a slightly association between chronic exposure to paraquat and asthma, and between several pesticide mixtures and particular spirometric symptoms and alterations. This suggests that workers exposed to mixtures containing paraquat should be closely monitored for respiratory disorders. In terms of the epidemiological methodology, future investigations that study pesticide mixtures using large sample sizes will make it possible to compare findings obtained from different statistical and mathematical methods in order to identify the most suitable method for measuring exposure.

Conflict of Interest

None declared.

Acknowledgements

The authors thank the workers who participated in the study and the environmental sanitation technicians at the Secretaries of Health in the municipalities of Carmen de Viboral, Granada and La Unión. The study was supported by the Colombian National Institute of Health and the Colombian Ministry of Health and Social Protection.

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