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Evaluating imidacloprid exposure among grape field male workers using biological and environmental assessment tools: An exploratory study

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Abstract

Imidacloprid is a neonicotinoid insecticide commonly injected through agricultural drip irrigation systems to reduce the population of vine mealybugs (*P. ficus*) in grape farms. There is a growing concern of potential human health effects of imidacloprid, however, there is limited information on the exposure to imidacloprid in farm workers. Imidacloprid exposure was evaluated in this exploratory study of 20 male migrant grape workers sampled five days after imidacloprid was injected in the irrigation system during winter and summer seasons. We administered a questionnaire on work activities, exposure characteristics, and socio-demographics and collected personal air, hand wipe, and spot urine samples. Heat exposure was also assessed. Spearman's correlation coefficients and Wilcoxon rank-sum tests were utilized to evaluate associations and differences in imidacloprid exposures with socio-demographic, occupational, and environmental characteristics. All participants had less than a high school education and about half identified an Indigenous language as their primary language. Although not detected in air samples, imidacloprid was detected in 85% of the hand wipes (median: 0.26: 0.41 μg/wipe, range: 0.05–7.10 μg/wipe). The majority of participants (75%) had detectable urinary concentrations of imidacloprid (median: 0.11 μg/g creatinine, range: 0.05–3.90 μg/g of creatinine), and nearly all (95%) had detectable urinary concentrations of 5-hydroxy-Imidacloprid (5-OH-IMI), a metabolite of imidacloprid (median: 1.28 μg/g creatinine, range: 0.20–27.89 μg/g creatinine). There was a significant correlation ($p < 0.001$) between imidacloprid in hand wipes and urinary imidacloprid and 5-OH-IMI (r_s: 0.67 for imidacloprid and 0.80 for 5-OH-IMI). Hand temperature was significantly and positively correlated ($p < 0.05$) with imidacloprid concentration on hand wipes (r_s: 0.70), and urinary biomarkers (r_s: 0.68 for imidacloprid, and 0.60 for 5-OH-IMI) suggesting that working in high temperatures may influence the exposure and absorption of imidacloprid. Thus, research on

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Declaration of competing interest

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farm workers would benefit in the future by evaluating imidacloprid exposure in relation to heat stress and other occupational factors.

Keywords

Neonicotinoids; Imidacloprid; Farm workers; Pesticide exposure; Occupational health

1. Introduction

In 2014, neonicotinoid insecticides accounted for more than 25% of the insecticide market, becoming the most extensively used insecticides worldwide (Bass et al., 2015; Englert et al., 2017; Zhang et al., 2019a). Neonicotinoids were developed to replace conventional organophosphates and pyrethroids because of their systemic properties (i.e. distributed throughout an entire plant), efficacy against a variety of insects, and their relatively low toxicity to mammals (Anderson et al., 2015; Tao et al., 2019). However, recent studies have shown growing concern about the possible adverse health effects that neonicotinoid insecticides may have on humans and other organisms (Cimino et al., 2016; Han et al., 2018). Furthermore, evidence suggests that neonicotinoids may be a threat to ecosystems due to their possible negative effect on wild humblebees and honey bee populations (Balfour et al., 2017; Rundlöf et al., 2015; Sánchez-Bayo et al., 2016; Tison et al., 2016; Whitehorn et al., 2012).

Within the neonicotinoid family, which includes acetamiprid, thiacloprid, clothianidin, thiamethoxam, and dinotefuran, imidacloprid is the most widely used neonicotinoid. Imidacloprid alone is used in over 120 countries on more than 140 agricultural crops, including rice, corn, potatoes, wheat, sugar, beets, cotton, fruits and turf (Elbert et al., 2008; Wang et al., 2015). Because of its abundant commercial usage, imidacloprid residues have been detected in different food matrices, in the environment, and even in drinking water (Klarich et al., 2017). Thus, with the increasing usage of imidacloprid, there is growing concern regarding potential health effects, as there is increased likelihood for humans to be exposed to imidacloprid via ingestion, dermal contact, and inhalation (Li and Jennings, 2017).

Several studies have found that imidacloprid exposure in mammals may be associated with the development of central nervous system diseases such as Parkinson’s disease, depression, and Alzheimer’s (Chen et al., 2014; Han et al., 2018). Other toxic effects observed in mammals with various pathways of exposure to imidacloprid have been related to developmental and reproductive outcomes (Cimino et al., 2016; Gu et al., 2013; Mesnage et al., 2018). Additionally, a recent study found that imidacloprid metabolites may have a greater mammalian toxicity than imidacloprid (Klarich Wong et al., 2019). While limited, a few epidemiological studies have shown positive associations with adverse birth outcomes and autism spectrum disorders, with imidacloprid usage and proximity of imidacloprid application (Keil et al., 2014; Yang et al., 2014). However, these studies based the exposure assessment on imidacloprid usage and not on imidacloprid biomarkers, or other more direct measurements of exposure.

Although there is an increasing number of studies researching the health effects associated with imidacloprid, there are very limited studies where human exposure to imidacloprid has been assessed. Some studies from Japan, Spain, China, Sri Lanka, and the United States (U.S.) have used biomonitoring techniques to evaluate the exposure to imidacloprid by measuring concentrations of imidacloprid and its metabolites in urine (López-García et al., 2017; Osaka et al., 2016; Ospina et al., 2019; Ueyama et al. 2014, 2015; Wang et al., 2015; Yamamuro et al., 2014; Zhang et al. 2019a, 2019b). Findings from some studies suggested that rural residents involved in agricultural activities, including their children, had higher imidacloprid detection frequencies and higher imidacloprid concentrations than people residing in urban areas (Tao et al., 2019; Wang et al., 2015). Interestingly, seasonality seems to play an important role in exposure to imidacloprid. For example, Ospina et al. (2019) reported the concentration of the imidacloprid metabolite 5-hydroxy-imidacloprid (5-OH-IMI) in urine was significantly higher in the summer than the winter in the general U.S. population (Ospina et al., 2019). Similarly, in a study of 223 three year old children in Japan, Osaka et al. (2016) reported the sum of all measured urinary neonicotinoids during the summer was significantly higher than in the winter (Osaka et al., 2016).

In addition to season, application timing and proximity to agricultural fields are likely other important factors in imidacloprid exposure. For example, two studies have reported significant increases in urinary imidacloprid concentrations in residents after spraying of imidacloprid in rural areas, reaching highest concentrations days after imidacloprid applications (Tao et al., 2019; Wang et al., 2015). Furthermore, rural adults and children had significantly higher concentrations of urinary imidacloprid after a nearby imidacloprid application compared to their urban counterparts (Tao et al., 2019; Wang et al., 2015). As with other pesticides, agricultural workers' direct contact with imidacloprid via application have been shown to result in agricultural workers exhibiting the highest concentrations of imidacloprid biomarkers (Tao et al., 2019). Agricultural workers' exposure to pesticides may also be increased by limited pesticide safety knowledge, mis- or non-usage of personal protective equipment (PPE), inadequate administrative workplace controls (e.g., lack of training), rate of pay, and educational/language barriers (Quandt et al., 2006). In addition, as with other pesticides, applicators' families may be exposed to imidacloprid via take-home pathways (Coronado et al., 2011; Lopez-Galvez et al., 2019).

To our knowledge, no other studies to date have evaluated imidacloprid exposure in grape workers even though imidacloprid is commonly applied in grape fields (Goulson, 2013; Mansour et al., 2010; Van Timmeren et al., 2012) through drip irrigation (Van Timmeren et al., 2012). Therefore, the objective of this study was to compare the exposure of grape field workers after imidacloprid has been applied via drip irrigation during the summer and winter season using urine biomarkers and environmental samples (air and hand wipes). Additionally, this study assesses the associations and differences between demographic, occupational, and environmental factors such as temperature contributing to imidacloprid exposure.

2. Methods

2.1. Study population and location

A convenience sample of 20 male migrant grape workers were recruited from a large commercial grape farm in Sonora, Mexico during the winter and summer seasons of 2016. This commercial grape farm mainly employs males (>95 percent) to work in the field, so we solely recruited male workers to participate in our study to achieve a representative sample of the overall farm population. The state of Sonora is known for its semi-arid and extreme heat environment with an average daily high temperature above 37.2 °C during the warm season (Eakin et al., 2007; Hallack-Alegria and Watkins Jr, 2007). Workers were contracted in their home states in southern Mexico and migrated to the farm by bus in February at the beginning of the harvest season. The contracted workers stayed at the farm through June–July, when the grapes were harvested and packaged in-field. Only farm workers, who worked in the fields and who did not directly apply or mix pesticides were considered for this study. A written consent in Spanish was obtained from participants. The University of Arizona Human Subjects Protection Program approved all study materials (IRB approval number: 1510159557). The analysis of coded samples at the Centers for Disease Control and Prevention (CDC) laboratory was determined not to constitute engagement in human subject research.

2.2. Sample collection

Timeframe and questionnaire: In this grape farm, field workers are usually not allowed in the field during any applications or for at least 24hrs after application of pesticides. The recommended restricted entry interval (REI) for imidacloprid in the United States is 12 h for soil application as well as foliar application (Nita et al., 2016). In this study, samples were collected 5 days after imidacloprid was applied to soil, well beyond the REI for imidacloprid. On-site agricultural engineers informed our research team when imidacloprid was to be applied in the grape farm. In 2016, 960 g/L of imidacloprid was injected equally via drip irrigation once in the summer and once in the winter. The drip irrigation for each row of grapes on the farm is pressurized by pumps responsible for delivering water to each individual grape vine with emission devices inserted in a drip hose (laterally). The hose is located approximately 0.3 m (1 foot) above ground level, dripping water containing pesticides at 2 to 3.5 L/h. The ground is visually wet during and after applications to obtain adequate soil moisture levels. All sample collection coincided with the imidacloprid application times. Questionnaires, biological specimens, and heat exposure measurements were collected during each of these two time points, exactly five days after each of the two imidacloprid applications. A face-to-face survey was administered in Spanish to each participant at the conclusion of their work shift. The survey included questions about experience in agriculture, time working at the current farm, knowledge of pesticides applied, training on pesticide safety and PPE, and general socio-demographic questions such as age, education, city/state of origin, and languages spoken.

Collection of Environmental and Urine Samples: Air samples were collected using personal sampling pumps with sorbent tubes that were clipped on workers' clothes in their breathing zone for the entirety of the work shift, approximately 8 h. Following NIOSH

method 5601, sorbent tubes containing XAD-2 absorbent were used and attached with flexible tubing to calibrated AirChek XR5000 pumps (SKC Inc., Eighty Four, PA, USA) with a flow rate set at 1 L/min (GAS, 1994). To avoid flow issues and pump malfunctions, the pumps were visually checked throughout the sampling process by the research team before sampling and during sampling in the grape fields. Handwipes, prewetted with 70% isopropanol (Twillwipes of 6 × 5 inches, M. G. Chemicals, Toronto, Ontario, Canada), were collected from each participant at the completion of the monitored work shift, before participants washed their hands (Deziel et al., 2011). One wipe was used to wipe the palmar surface, dorsal surface, the surface between digits, and the lateral surfaces of each participant's hand. Each wipe was in contact with hand skin surface for approximately 30 s in total. The wipes were then put inside a sealed glass amber jar to be transported and stored. For quality assurance and quality control (QA/QC) purposes, air and wipe field blank samples were collected. The day after collecting air and handwipe samples, first morning void urine samples were collected for each participant. Details on urine collection are presented elsewhere (Lopez-Galvez et al., 2018). The urine, hand wipe, and sorbent tube samples were transported by car for approximately 5 h in a cooler with ice and stored frozen in the University of Arizona Medical Research Building laboratory until shipment for analysis.

Heat Stress: Heat exposure was assessed by collecting relative humidity, dry bulb temperature (also known as ambient temperature), and globe temperature using a handheld wet-bulb globe temperature (WBGT) monitor (HT30 Heat Stress WBGT Meter, Extech, Nashua, NH) throughout the workday near the participants' working areas in the field. Dry-bulb temperature is a measure of air temperature unaffected by moisture, while globe temperature is a measure of the environmental radiant heat and convective heat from ambient air, which was collected with a sensor placed inside of a 40 mm diameter copper ball that is painted black (ISO, 2017). The WBGT is one of the most appropriate procedures to evaluate the effect of heat on a person during a workday and has been approved by the International Organization for Standardization (ISO). Using guidelines from the American Conference of Governmental Industrial Hygienists (ACGIH), workers' clothing type was observed and added to the effective WBGT ($WBGT_{eff}$). The metabolic rate was estimated using the Table for Metabolic Rate Categories set by the ACGIH guidelines and it was determined from recorded observations of participants' working speed, body movement, tool usage, and mobility while working in the field (ACGIH, 2017). In addition, hand temperature was collected with a Fluke 62 MAX handheld infrared thermometer (Fluke Corp, Washington, USA) at the end of workers' shift before collecting hand wipe samples.

2.3. Laboratory analysis

Sorbent tubes from personal air samples were analyzed for imidacloprid by Bureau Veritas/Clayton Group Services, Inc. using solid-phase extraction high-performance liquid chromatography-isotope dilution tandem mass spectrometry (HPLC-MS/MS) according to modified NIOSH method 5601 (GAS, 1994). Following the QA/QC protocol in NIOSH method 5601, a laboratory control sample was prepared for every 10 air samples collected and an unspiked sampler was included as a laboratory blank. The air samples were analyzed along with the liquid standards, field and laboratory blanks. The limit of detection (LOD) for

imidacloprid in air samples was 0.50 μg/m^3. The imidacloprid concentration on hands wipes was determined by Environmental Micro Analysis (E.M.A. Inc.) laboratory in Woodland, California. Approximately 50 g of homogenized sample were extracted with acetonitrile (100 ml), which was filtered to continue with the solid phase extraction clean up. The final extracts were analyzed for imidacloprid using liquid chromatography-tandem mass spectrometry (LC/MS/MS).To ensure quality data, the collected wipes were analyzed in parallel with two field blanks and two reagent (lab) blanks. The LOD for imidacloprid was 0.01 μg/wipe.

Urine samples were analyzed for six neonicotinoid biomarkers at the National Center for Environmental Health (NCEH) at the CDC in Atlanta, GA, USA. Four were parent neonicotinoids: acetamiprid, clothianidin, imidacloprid, and thiacloprid; two were neonicotinoid metabolites: 5-OH-IMI, and acetamiprid-N-desmethyl. Clothianidin is also a metabolite of thiamethoxam, another neonicotinoid insecticide. Details of the analytical method are described elsewhere (Baker et al., 2019). Briefly, the biomarkers were extracted from 200 μL of urine by online solid phase extraction, separated by reversed phase high-performance liquid chromatography, and detected with isotope dilution-electrospray ionization tandem mass spectrometry (Baker et al., 2019). LODs were 0.30 μg/L (acetamiprid), 0.20 μg/L (5-OH-IMI, clothianidin, acetamiprid-N-desmethyl), 0.05 μg/L (imidacloprid), and 0.03 μg/L (thiacloprid). The CDC laboratory is certified by the Health Care Financing Administration to comply with the quality control/quality assurance requirements set forth in the Clinical Laboratory Improvement Act of 1988 (CLIA ‘88). Therefore, the analytical measurements followed strict CLIA-recommended guidelines. Each analytical run included study samples, calibration standards, two high- and two low-concentration QC materials (prepared using pooled human urine), and blanks to ensure data accuracy and reliability. The concentrations of QCs, averaged to obtain one measurement of high-concentration QC and low-concentration QC for each run, were evaluated using standard statistical probability rules (Caudill et al., 2008). If the QC samples failed the statistical evaluation, all study samples in the run were re-extracted. Urine biomarker concentrations were adjusted for creatinine (Organization, 1996). Creatinine was measured at the University of Arizona Medical Research Building laboratory using Creatinine Assay Kits (R&D Systems, Minneapolis, MN, USA), and analyzed with an EL × 808™ Absorbance Microplate Reader (BioTek Instruments, Winooski, VT, USA).

2.4. Data analysis

Descriptive statistics were performed to describe target analytes concentrations in urine, hand wipes, and air samples. For concentrations below the LOD, the LOD/√2 was assigned (Hornung and Reed, 1990). The questionnaire data were transcribed and managed using Research Electronic Data Capture (REDCap) tools hosted at the University of Arizona (Harris et al., 2009). Descriptive statistics were also used to summarize occupational and socio-demographic characteristics. Spearman’s correlation coefficients were calculated to assess relationships between urine biomarkers, insecticide concentration in hand wipes, hand temperature, and age. Wilcoxon rank-sum tests were used to evaluate insecticide concentration differences between seasons. Correlations and differences were evaluated only if the detection frequency of the analyte was greater than 50%. In addition, associations

of insecticide concentrations with socio-demographic and occupational characteristics were evaluated using Wilcoxon rank-sum tests and Spearman's correlations for dichotomous and continuous variables as appropriate. The data analyses were conducted using STATA V.13. and R studio software (StataCorp, 2013; Team, 2015).

3. Results

All participants were male migrants from the state of Chiapas, Mexico. Their mean age was 26.4 years. About half (45%) of the participants reported speaking an Indigenous language as their primary language and a large portion (70%) did not attend high school or above. Detailed demographic information is presented elsewhere (Lopez-Galvez et al., 2018).

Environmental and Urine samples:

As presented in Table 1, approximately 75% of the hand wipes had detectable imidacloprid levels. Imidacloprid concentration in hand wipes ranged from 0.05 to 7.10 μg/wipe. Imidacloprid was not detected in the air samples. 5-OH-IMI, a metabolite from imidacloprid, was detected in 95% of urine samples with a concentration range of 0.15–27.98 μg/g creatinine; imidacloprid was detected in 65% of the urine samples with a concentration range of 0.05–3.90 μg/g of creatinine. Clothianidin was detected in 40% of the urine samples with concentrations ranging from 0.25 to 2.39 μg/g creatinine. The acetamiprid metabolite, acetamiprid-N-desmethyl, was only detected in one participant's urine sample at a relatively low concentration, while acetamiprid and thiacloprid were not detected in any urine samples. Clothianidin, acetamiprid and thiacloprid were not considered for any statistical tests because of their low detection frequencies.

Occupational characteristics in relation to imidacloprid exposure:

Participants' heat stress was higher in the summer season compared to the winter(Table 2). After adding the work clothing factor, the mean $WBGT_{eff}$ was nearly 10 °C higher in summer than in winter. When combining the observed metabolic rate with $WBGT_{eff}$, most worker's heat stress levels during the summer surpassed the Action Limit and Threshold Limit Values (TLV) recommended by ACGIH, which was not the case during the winter (ACGIH, 2017). The temperatures measured on hand surfaces were significantly higher in summer than in winter (Wilcoxon rank-sum, $p < 0.05$).

As presented in Table 3, participants who received training on PPE had significantly lower imidacloprid concentration in hand wipes than participants who did not receive any training (Wilcoxon rank-sum, $p < 0.05$). For 5-OH-IMI and imidacloprid in urine, although not statistically significant, concentrations were lower for participants who received training on PPE usage in comparison to participants with no PPE training. Although over half of the workers (60%) reported having received training on PPE usage, none of the participants were observed wearing gloves during the work-shift, but all covered their face with a shirt or bandana throughout their work-shift. In addition, participants who reported speaking an Indigenous language as their primary language had significantly higher urinary 5-OH-IMI and imidacloprid and imidacloprid handwipe concentrations than participants who only spoke Spanish (Wilcoxon rank-sum, $p < 0.05$). Additionally, participants who did not attend

high school had significantly higher urinary concentrations of imidacloprid and 5-OH-IMI than participants that attended high school or above (Wilcoxon rank-sum, $p < 0.05$). In the summer, imidacloprid concentration in handwipes and urine (imidacloprid and 5-OH-IMI) were significantly higher (Wilcoxon rank-sum, $p < 0.001$) than in the winter. It is important to mention that participants exceeded the heat stress ACGIH Action Limit during their work shifts in the summer (average $WBGT_{eff}$: 26.5 °C) compared to participants during the winter season (average $WBGT_{eff}$: 16.7 °C) (Table 3).

In addition, as illustrated in Fig. 1, the urinary imidacloprid and 5-OH-IMI concentrations (μg/g of creatinine) were significantly higher (Wilcoxon rank-sum test, $p < 0.05$, $p < 0.001$) during the summer than winter season. Similarly, the imidacloprid concentrations measured on workers' hand wipes were also significantly higher (Wilcoxon rank-sum test, $p < 0.05$, $p < 0.01$) in summer compared to the winter season. As presented in Fig. 2, urinary 5-OH-IMI was strongly correlated with urinary imidacloprid and the concentration of imidacloprid in handwipe samples (r_s: 0.80 and 0.85; $p < 0.001$). There was a moderate correlation between hand temperature and urinary 5-OH-IMI (r_s: 0.60; $p < 0.05$). Similarly, urinary imidacloprid was moderately correlated with the concentration of imidacloprid in handwipes (r_s: 0.67; $p < 0.05$) and hand temperature (r_s: 0.68; $p < 0.001$).

4. Discussion

To our knowledge, this is the first study to evaluate farm workers' exposure to neonicotinoids in the Americas. Urinary 5-OH-IMI was detected in 95% of samples compared to only 65% for urinary imidacloprid, suggesting that 5-OH-IMI may be a better urinary marker of imidacloprid exposure than its parent compound. This finding is supported by the results reported by Ospina et al. (2019), in which 5-OH-IMI was detected more frequently than its corresponding parent compound in the U.S. general population (20% and 5%, respectively) (Ospina et al., 2019). The urinary median concentrations of 5-OH-IMI and urinary imidacloprid in the present study were higher than those of the U.S. general adult population, as presented in the 2015–2016 National Health and Nutrition Examination Survey (Ospina et al., 2019). On the other hand, the median urinary imidacloprid concentration in our study (0.27 μg/L) was similar to the results reported in a recent survey conducted in China (0.21 μg/L) (Zhang et al., 2019b). In comparison to other studies in rural regions, our imidacloprid values were generally higher than samples taken from a rural area of China, but lower than a study exploring Chinese pesticide applicators and residents living near orchard fields (Tao et al., 2019; Wang et al., 2015). The concentration of urinary imidacloprid collected from rural male participants living nearby orchard fields and the male pesticide applicators reported by Tao et al. (2019) were 4.46 and 4.88-fold higher, respectively, than our study 95th percentile concentrations. This suggests that spraying events may lead to direct contact of sprayers while residents nearby may be exposed via pesticide drift or the take-home route of exposure. Several of these factors, however, are absent in our study population, because imidacloprid was applied through the drip irrigation system. It is also important to mention that in Tao et al. (2019), samples were collected from participants only 2 days after pesticides were hand sprayed by applicators. The observed differences in urinary pesticide concentrations is likely explained by the differences in application methods (drip irrigation in the present study vs. hand spraying in

Tao et al. (2019)) and time since application (5 days in the present study vs. 2 days reported by Tao et al. (2019).

Although urinary 5-OH-IMI was detected more frequently and at higher concentrations than urinary imidacloprid in our current study, it is difficult to compare our results; there are no other farm workers studies that have utilized 5-OH-IMI as a biomarker. Even though pesticide applicators may experience higher exposures than field workers, field workers are in constant direct contact with the crops (Gatto et al., 2016), so it is important to also understand their exposures. Hence, there is a need for a similar comparison group and a need to conduct additional studies on farm workers' exposure to neonicotinoids after application via drip-irrigation. All imidacloprid measurements, including those from urinary metabolites and hand wipes, were significantly positively correlated with each other (r_S: 0.66 to 0.85, $p < 0.05$), suggesting a common source. Strong correlations between imidacloprid concentrations on hand wipes with urinary 5-OH-IMI suggest that the primary source of exposure to imidacloprid in this population may come from workers' environment, perhaps from contact with the grape plant leaves/fruit, soil, or irrigation water, and not food intake (Schoning and Schmuck, 2003). It is important to mention that no participant was observed wearing gloves while working, which could influence an increase in dermal exposure and the overall urinary concentrations. Thus, hand wipes should be explored as a possible, effective, and less intrusive surrogate than urinary biomarkers to assess exposure. To our knowledge, this is the first study to characterize farm workers' dermal exposure to imidacloprid using hand wipes. It is important to mention that inhalation may be a route of exposure, however, the air concentrations were below the detection limit of the method in the current exploratory study. These results support the work of Cao et al. (2015) who found that agricultural workers' exposure to imidacloprid through inhalation was less than 1% of the total exposure (Cao et al. 2015, 2018).

Heat stress and dermal exposure to imidacloprid:

The heat stress levels of participants exceeded the respective ACGIH Action Limit and ACGIH TLV during summer, which may have resulted in heat strain, the overall physiological response that can result from heat stress. The heat stress suffered by migrant workers during the summer season may have influenced the absorption of imidacloprid, as we found significantly ($p < 0.001$) higher detection and concentrations of urinary 5-OH-IMI and imidacloprid on handwipes during summer compared to winter. Similar findings with respect to seasonal (summer vs. winter) variance in urinary neonicotinoid markers were found in other studies, which were attributed to the possible different volumes of insecticides applied during warmer months, as pests may increase with higher temperatures (Meineke et al., 2013; Osaka et al., 2016; Ospina et al., 2019). However, in the current study, imidacloprid was known to be applied in the field via the irrigation system in equal concentrations for summer and winter, and the exposure was assessed within the same timeframe (5 days after pesticide injection) for both seasons. Additionally, the significant positive correlation observed between hand temperature and the urinary neonicotinoids biomarkers detected in this study suggested that, at higher temperatures, the insecticides applied in the drip irrigation could be directly associated with the amounts absorbed by the body.

The high summer temperatures can play an important role in the plant's uptake and distribution of imidacloprid from soil to leaves, and potentially increase the exposure of imidacloprid to farm workers (Bonmatin et al., 2015). Because imidacloprid is a water-soluble insecticide that circulates systemically within the plant, higher imidacloprid concentrations could be present on grape leaves during sunnier and warmer conditions, as previous studies have shown that the water in guttation drops (plants exudation of drops on leaves' edges) may evaporate in high temperatures, incrementing the concentration of imidacloprid on the leaves (Bonmatin et al., 2015; Tapparo et al., 2011). Thus, high levels of imidacloprid on plant leaves could have potentially increased the imidacloprid levels found on workers' hand wipes during the summer. Seasonal differences have been reported in other pesticide exposure studies, including those exploring organophosphate and pyrethroids in children and farm worker populations (Arcury et al., 2009; Freeman et al., 2004). Changes in dietary intake and food availability by season, agricultural crop rotation, residential usage, weather-related insect activity, and pet ownership may explain seasonal differences in pesticide exposure (Lu et al. 2008, 2009). Thus, further research is needed to explore the relationship between seasonality and imidacloprid exposure.

In this exploratory study, several demographic and occupational factors were found to influence exposure to imidacloprid in this population. For example, although the observed level of PPE usage was limited to face covering and gloves were not worn, our results suggest that increasing PPE training could reduce imidacloprid exposure for grape workers, as the concentrations of imidacloprid in handwipes and urine were lower in participants who received some sort of PPE training. There is substantial evidence in the scholarly literature supporting the importance of training programs incorporating PPE as a method to reduce pesticide exposure in farm workers. (Baldi et al., 2006; MacFarlane et al., 2013; McCauley et al., 2013; Quandt et al., 2013; Salvatore et al., 2015; Thouvenin et al., 2016). Pesticide exposure can also be reduced by substitution or elimination of ingredients that pose health risks, implementation of administrative controls such as worker rotation, increased time before workers can re-enter fields, and frequent health and safety trainings. An effective alternative to the use of imidacloprid to control mealybugs is the introduction of biological controls in grape fields such as parasitoids and predators (Mani and Shivaraju, 2016). Additionally, our findings showed that the imidacloprid concentrations varied significantly depending on participants' level of education and primary language. The higher imidacloprid levels in urine and handwipes in grape workers who spoke an Indigenous language as their primary language compared to other grape workers suggests that pesticide safety and exposure trainings should incorporate farm workers' educational level and language of preference to reduce pesticide exposure.

One of the limitations of this study is the small sample size and the participation of only male workers can affect the generalizability of the findings to female workers. Another limitation is the use of only WBGT to measure heat stress, as a clearer and more accurate assessment could involve measuring individual heat stress using personal sampling devices or sensors. The lack of information on dietary data is an important limitation, as some of the neonicotinoid exposure may have occurred via ingestion. For example, a dietary log or survey of food products consumed by workers could have helped determine food sources containing imidacloprid and the percentage/proportion of exposure attributed to

dietary vs. other routes of exposure. Without knowing the dietary contribution to overall exposure, we cannot rule out diet as a contributing factor. The urinary biomarkers allow us to examine the overall exposure to imidacloprid and its metabolites. Participants in our study were exposed to imidacloprid-like insecticides, either through the parent compound or its metabolites via dietary ingestion, non-dietary ingestion, dermal absorption, and/or less likely though inhalation. Another limitation is being unable to compare with other farm worker populations within the region or a control group of non-farmworkers to better understand background neonicotinoid levels in the region.

While the sample size of this exploratory study was small, we are confident that the imidacloprid concentrations measured confirm that grape workers in this region might be exposed to imidacloprid during their workday in two different seasons. An important strength of this exploratory study is that exposure to imidacloprid in grape workers was evaluated by not only using urinary biomarkers, but also assessed imidacloprid levels in air and handwipes. Last, this is the first study to explore the relation of heat stress and imidacloprid exposure in field workers. Although one could suggest that the observed increase of imidacloprid concentrations is due to high levels of heat stress, additional studies are merited.

5. Conclusion

This study suggests that imidacloprid exposure may be common among grape field workers. The urinary concentrations of imidacloprid in these workers were higher than in the general U.S. population, but lower than those reported in pesticide applicators in studies from other regions. This study showed that temperatures and variations in seasonal applications may play an important role in exposure to imidacloprid and suggest higher exposures in the summer even though the same amount of imidacloprid was applied in the field in both seasons. Also, increased hand temperature was associated with higher imidacloprid levels on hand wipes and urinary imidacloprid metabolites. Therefore, assessing the relationship between heat stress and imidacloprid exposure in relation to increasing temperatures would increase our understanding of their potential relevance to outdoor workers' exposures. Additionally, special care should be taken to reduce pesticide exposure in vulnerable populations, including migrant and seasonal workers whose primary language may not be the language spoken at the location of work.

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Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC). Use of trade names is for identification only and does not imply endorsement by the CDC, the Public Health Service, or the US Department of Health and Human Services.

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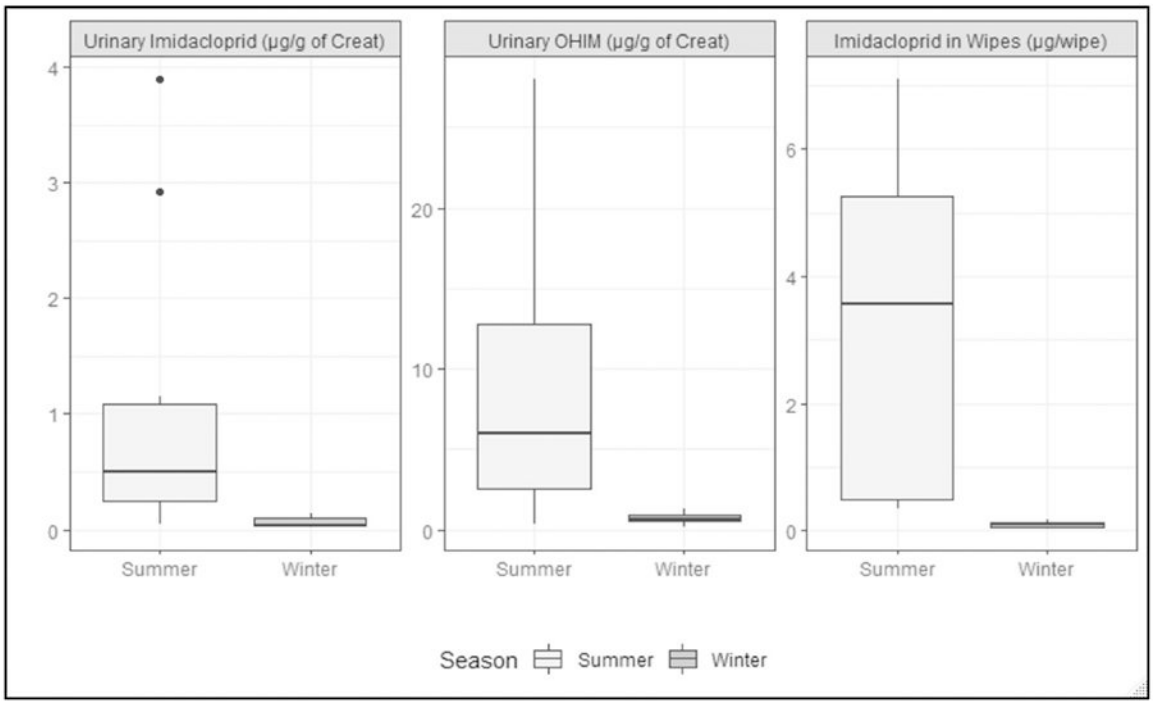

Fig. 1.

Comparison of imidacloprid biomarkers in urine and imidacloprid in hand wipes by season. Biomarkers concentrations were significantly different (Wilcoxon rank-sum test, $p < 0.05$) between summer and winter.

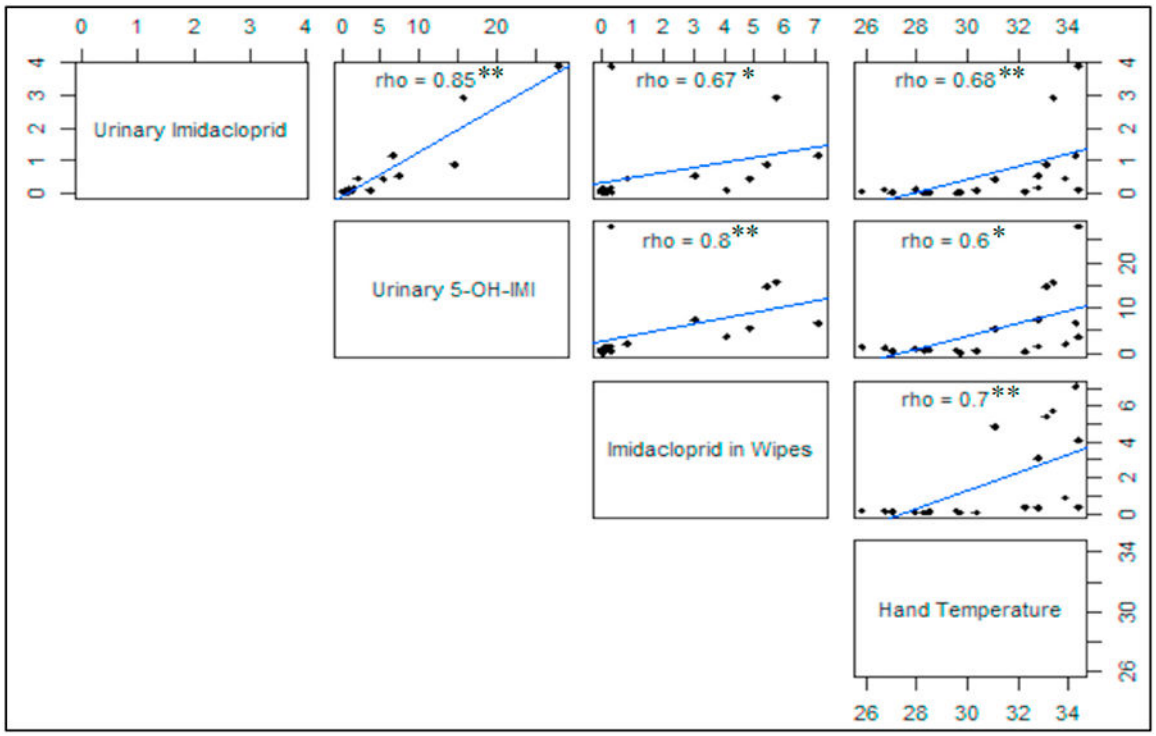

Fig. 2.

Spearman correlations among urinary imidacloprid, urinary 5-hydroxy imidacloprid (5-OH-IMI), imidacloprid in handwipes, and hand temperature. Significant correlations: **< 0.05; ***< 0.001.

Table 1

Neonicotinoid parent and metabolite concentrations in urine samples, and environmental media (hand wipes and air samples), n=20.

Environmental samples								
Insecticide Parent Compound	**Environmental Media**	**LOD (µg)**	**Detection n (%)**	**Range (µg/wipe)**	**25th**	**Median**	**75th**	**95th**
Imidacloprid	Hand wipes	0.01	15 (75)	0.05–7.10	0.12	0.26	3.31	5.79
Imidacloprid	Air	0.50	ND	–	–	–	–	–
Urine samples								
Insecticide	**Urinary Metabolite(s)**	**LOD (µg/L)**	**Detection n (%)**	**Range (µg/g creatinine)**	**25th**	**Median**	**75th**	**95th**
Imidacloprid	5-Hydroxy-imidacloprid (5-OH-IMI)	0.20	19 (95)	0.20–27.98	0.62	1.28	5.73	16.29
	Imidacloprid	0.05	13 (65)	0.05–3.90	–	0.11	0.48	2.97
Clothianidin & Thiamethoxam	Clothianidin	0.20	8 (40)	0.25–2.39	–	–	0.63	1.32
Acetamiprid	Acetamiprid-N-desmethyl	0.20	1 (5)	LOD - 1.56	–	–	–	–
	Acetamiprid	0.30	0	-	-	-	-	-
Thiacloprid	Thiacloprid	0.03	0	–	–	–	–	–

Abbreviations: g, grams; L, liters; LOD, limit of detection; n, sample size; ND, not detected; µg, microgram.

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Table 2

Heat stress assessment and hand temperature results by season (n = 20).

		Winter				
		Dry bulb Temperature (°C)	**Globe Temperature (°C)**	**Relative Humidity (%)**	**$WBGT_{eff}$ (°C)**	**Hand Temperature (°C)**
Metabolic Rate Range 180–300 W	Min	18.3	21.4	12.8	13.9	25.9
	Max	25.7	42.6	24.4	20	30.4
	Mean	22.2	31.4	20.2	16.7	28.1
	SD	2.6	7.1	4.1	2.1	1.5
		Summer				
		Dry bulb Temperature (°C) *	**Globe Temperature (°C)**	**Relative Humidity (%) ***	**WBGTeff (°C) ***	**Hand Temperature (°C) ***
Metabolic Rate Range 180–415 W	Min	31.0	35.7	28	23.8	31.1
	Max	36.4	48.8	35.8	29.7	34.4
	Mean	33.6	41.1	32.4	26.5	33.3
	SD	2.7	5.2	2.6	2.2	1.1

Abbreviations: °C, Celsius; SD, standard deviation; W, watts; $WBGT_{eff}$, effective wet bulb globe temperature

* Significant differences ($p < 0.05$) between summer and winter seasons (Wilcoxon rank-sum test).

Table 3

Demographic and occupational characteristics related with imidacloprid exposure.

Characteristics	n (%)	Urinary Imidacloprid, Median (μg/g creatinine)	Urinary 5-OH-IMI, Median (μg/g creatinine)	Dermal Imidacloprid, Median (μg/wipe)
Agricultural experience				
Less than or equal than five years	9 (45)	0.11	1.35	0.35
More than five years	11 (55)	0.12	1.22	0.17
Time working in this grape field				
Less than or equal than 3 months	7 (35)	0.45	5.42	4.09
More than 3 months	13 (65)	0.10	0.73	0.13
Know which pesticides are applied in the fields				
No	15 (75)	0.11	1.22	0.17
Yes	5 (25)	0.18	1.57	0.35
Received training on how to reduce pesticide exposure in this field				
No	14 (70)	0.11	1.10	0.15
Yes	6 (30)	0.12	1.50	0.35
Received training on PPE usage				
No	8 (40)	0.45	4.57	3.58
Yes	12 (60)	0.10	0.85	0.15 *
Washes work clothes with leisure clothes				
No	6 (30)	0.12	2.34	0.21
Yes	14 (70)	0.10	1.29	0.26
Wears same work clothes for more than two consecutive days without washing it				
No	5 (25)	0.10	0.80	0.08
Yes	15 (75)	0.11	1.50	0.35
Primary language				
Spanish	11 (55)	0.05	0.70	0.13
Indigenous	9 (45)	0.50 **	5.42 **	3.10 *
Education				
Below high school	14 (70)	0.13	1.68	0.35
High school and above	6 (30)	0.08 *	0.10 *	0.13

Characteristics	n (%)	Urinary Imidacloprid, Median (μg/g creatinine)	Urinary 5-OH-IMI, Median (μg/g creatinine)	Dermal Imidacloprid, Median (μg/wipe)
Heat stress by season (WBGT)				
Winter season: 16.7	10 (50)	0.05	0.65	0.11
Summer season: 26.5	10 (50)	0.49 **	6.04 **	3.58 **

Abbreviations: 5-OH-IMI, 5-Hydroxy imidacloprid in urine (an imidacloprid metabolite), WBGT, average wet-bulb globe temperature by season

* Significant differences (Wilcoxon rank-sum test: < 0.05

** < 0.001).