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Exposure to Neonicotinoid Insecticides in the U.S. General Population: Data from the 2015–2016 National Health and Nutrition Examination Survey

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Abstract

Background: Neonicotinoids are used for insect control in agriculture, landscaping, and on household pets. Neonicotinoids have become popular replacements for organophosphate and carbamate insecticides, and use is on the rise.

Objectives: To assess human exposure to neonicotinoid insecticides in a representative sample of the U.S. general population 3 years and older from the 2015–2016 National Health and Nutrition Examination Survey (NHANES).

Methods: We used online solid-phase extraction coupled to isotope dilution high-performance liquid chromatography-tandem mass spectrometry after enzymatic hydrolysis of conjugates to quantify in 3,038 samples the urinary concentrations of six neonicotinoid biomarkers: four parent compounds (acetamiprid, clothianidin, imidacloprid, thiacloprid) and two metabolites (N-desmethyl-acetamiprid, 5-hydroxy-imidacloprid). We calculated distribution percentiles, and used regression models to evaluate associations of various demographic parameters and fasting time with urinary concentrations above the 95th percentile (a value selected to represent higher than average concentrations) of neonicotinoid biomarkers.

Results: Weighted detection frequencies were 35% (N-desmethyl-acetamiprid), 19.7% (5-hydroxy imidacloprid), 7.7% (clothianidin), 4.3% (imidacloprid), and <0.5% (acetamiprid, thiacloprid). The weighted frequency of having detectable concentrations of at least one of the six biomarkers examined was 49.1%. The 95th percentiles for N-desmethyl-acetamiprid, 5-hydroxy imidacloprid, and clothianidin were 1.29, 1.37, and 0.396 μg/L, respectively. For people who fasted <8 hours, regardless of race/ethnicity and sex, 3–5 year old children were more likely to have N-desmethyl-acetamiprid concentrations above the 95th percentile than adolescents (adjusted odds ratio (OR) = 3.12; 95% confidence interval [CI], (0.98-9.98)) and adults (adjusted OR = 4.29; 95% CI, (2.04-9.0)); and children 6–11 years of age were more likely than adults to have N-desmethyl-acetamiprid concentrations above the 95th percentile (adjusted OR = 2.65; 95% CI, (1.2-5.84)). Asians were more likely than non-Asians to have concentrations above the 95th

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percentile of N-desmethyl-acetamiprid (adjusted OR = 1.94; 95% CI, (1.08-3.49)) and 5-hydroxy-imidacloprid (adjusted OR = 2.25; 95% CI, (1.44-3.51)). Samples collected during the summer were more likely to have metabolite concentrations above the 95th percentile than those collected in the winter (adjusted OR 1.55 for N-desmethyl-acetamiprid, and 2.43 for 5-hydroxy-imidacloprid).

Conclusions: The detection of neonicotinoid metabolites more frequently and at much higher concentrations than the corresponding parent compounds suggests that the metabolites may be suitable biomarkers to assess background exposures. About half of the U.S. general population 3 years of age and older was recently exposed to neonicotinoids. Compared to other age ranges and ethnicities, young children and Asians may experience higher exposures. At present, reasons for such differences remain unknown.

1. Introduction

Neonicotinoids are synthetic insecticides used for pest control in agriculture [1–4], landscaping [5,6], and for treating domestic animals [7]. The neonicotinoid market expanded rapidly since their introduction in the early 1990‘s mainly due to their broad spectrum of efficacy, systemic action, pronounced residual activity, unique mode of action and versatile uses and applications [8]. Between 2003–2011 neonicotinoid use increased rapidly as seed application products were introduced in field crops such as maize, soybeans, wheat and cotton [1]. In 2011, 34-44% of soybeans and at least 79% of the corn planted in the USA were treated with neonicotinoids [1,9]. By 2014, neonicotinoids held more than 25% of the global insecticide market [10]. Because of their low acute mammalian toxicity, compared to older insecticides [7], which have developed resistant insect strains and have increased restrictions based on human safety considerations, neonicotinoids have been increasingly replacing organophosphates, methylcarbamates, and pyrethroids [11]. The neonicotinoid family includes acetamiprid, clothianidin, imidacloprid, thiacloprid, nitenpyram, dinotefuran, and thiamethoxam.

Neonicotinoids are broadly detected in the ecosystem; they were detected in soils [12–16] where half-lives varied from a few days to several years, depending on the compound, and can accumulate in soil when used repeatedly [2,12]. Because of their relatively high water solubility, neonicotinoids are prone to leaching into waterways [2]; they have been detected in surface, ground and drinking waters [17–23]. Additionally, neonicotinoids were also found in raw and treated sewage [24], house dust [25], the livers of wild turkeys [26], and in several organs from white-tailed deer [27]. Scrutiny on the use of neonicotinoids has increased [2,18,22,28–30] because of the known environmental risks of these compounds (e.g., insecticide resistance, impact on pollinators [31] and insectivorous birds [32]).

Neonicotinoids have high affinity for nicotine acetylcholine receptors (nAchRs) located within insects’ central nervous system. Neonicotinoids work by opening the ion channels which allow the entry of Na^+ and Ca^{2+} into cells [33], causing excitation, trembling, paralysis, and death depending on dose and exposure time [2,34]. In vertebrates, neonicotinoid toxicity is considered low because of the relatively low affinity of the nAchRs and poor penetration of the blood–brain barrier [35]. However, recent studies suggest

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potential toxic effects of neonicotinoids to mammals, and even humans, including cytotoxicity, genotoxicity, reproductive effects, neurotoxicity, immunotoxicity, hepatotoxicity and hepatocarcinogenicity [27,36–39]. Additionally, although reports of acute poisoning cases in humans are scarce [40–43], such poisonings may have increased with the wider application of neonicotinoid insecticides [42].

A potential route of human exposure to neonicotinoids is diet [37]. Because neonicotinoids are taken up by the plant and transported throughout it (e.g., leaves, flowers, roots, stems, pollen, nectar), they cannot be washed off easily from food [44] and have been detected in honey, fruits, vegetables, cereals, grape berries, grape leaves, and tea leaves [15,44–48]. Detection frequencies of neonicotinoids in the urine of Japanese women increased significantly between 1994 and 2011 [49], suggesting that exposure is related to intake because neonicotinoids use increased significantly during that period in Japan. Similar data in the United States do not exist.

Neonicotinoids can be metabolized by phase I enzymes [50,51] and some of these phase I neonicotinoid metabolites can undergo phase II conjugation [52,53] to facilitate elimination. Although currently there are no human in-vivo metabolism studies with neonicotinoids, in vitro studies with imidacloprid identified 5-hydroxy-imidacloprid, an oxidation product, as the major metabolite [54]. N-desmethyl-acetamiprid was the main metabolism product of acetamiprid in rats [55], and was detected in 86.6 to 93.5% of urine specimens from a study involving 46 Japanese children [56]. Imidacloprid, acetamiprid, 5-hydroxy-imidacloprid and N-desmethyl-acetamiprid were identified in the urine of patients suspected of neonicotinoid pesticide poisoning [51,57]. Therefore, these metabolites could be used as potential biomarkers of human exposure.

Measuring the concentrations of neonicotinoids and/or their metabolites (e.g., exposure biomarkers) in human samples can contribute to better understanding of human exposure and exposure sources, description of time trends, and potential impacts of regulations on the use of neonicotinoids. We recently developed an analytical method to measure urinary concentrations of six neonicotinoid biomarkers including four parent compounds (acetamiprid, clothianidin, imidacloprid, and thiacloprid) and two metabolites (N-desmethyl-acetamiprid, and 5-hydroxy-imidacloprid) [58]. Here, we report for the first time the concentrations of these biomarkers in a representative sample of the U.S. general population 3 to 80 years of age from the 2015–2016 National Health and Nutrition Examination Survey (NHANES).

2. Materials and Methods

2.1. Study Population

NHANES is the result of the National Health Survey Act of 1956, which granted legislative authorization for a continuing survey to provide current statistical data on the amount, distribution, and effects of illness and disability in the United States [59]. NHANES, conducted continuously since 1999 by the National Center for Health Statistics (NCHS) at the Centers for Disease Control and Prevention (CDC), includes direct household interviews with demographic, socioeconomic, dietary, and health-related questions, physical

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examinations, and collection of biological samples. Some of these samples are used to assess exposure to environmental chemicals.

For this study, we analyzed 3,038 spot urine samples collected from the following 2015–2016 NHANES participants: all children 3–5 years of age (N=505), and a random one-third subsample of participants six years of age and older (N=2,533). NCHS Research Ethics Review Board reviewed and approved the study protocol. All adult respondents gave informed written consent to participate in the survey; parents or guardians provided written permission for participants younger than 18 years. Youth 7–17 years of age provided assent to participate in the survey [60].

2.2. Urinary Concentrations of Neonicotinoid Biomarkers and Creatinine Measurements

The specimens were collected at the NHANES mobile examination center (MEC), and, within hours of collection, urine was aliquoted and frozen at the MEC. The frozen urine containers were shipped on dry ice to the CDC‘s National Center for Environmental Health where they were stored at −70 °C until analysis. We quantified acetamiprid, clothianidin, imidacloprid, thiacloprid, N-desmethyl-acetamiprid, and 5-hydroxy-imidacloprid. The analytical method, described in detail elsewhere [58], relies on an enzymatic hydrolysis of urinary conjugates of the target biomarkers in 200 μL urine, online solid phase extraction, separation by reversed phase high-performance liquid chromatography, and detection by isotope dilution-electrospray ionization tandem mass spectrometry. The precision of measurements, expressed as the relative standard deviation of multiple measures of urine-based quality control (QC) materials, ranged from 3.7% to 10.2%, depending on the biomarker and concentration. The method accuracy, calculated from the recovery at three spiking levels (1.6, 6.3, and 25 ng/mL), ranged from 91.2% to 116%, depending on the analyte and concentration [58]. The limits of detection (LODs) were 0.03 μg/L (thiacloprid), 0.2 μg/L (N-desmethyl-acetamiprid and clothianidin), 0.3 μg/L (acetamiprid), and 0.4 μg/L (imidacloprid and 5-hydroxy-imidacloprid).

An analytical run included 12 calibration standards, two reagent blanks, two low and two high urine based quality control (QC) materials and up to 72 NHANES study samples as described in detail elsewhere [58]. The analytical measurements followed strict quality control/quality assurance protocols to ensure data accuracy and reliability [61]. If the QC samples failed the statistical evaluation, all of the study samples in the run were re-extracted.

Urinary creatinine concentrations were determined using a commercially available enzymatic assay (Roche Cobas 6000, Roche Diagnostics, Indianapolis, IN) [62].

2.3. Statistical Analysis

We analyzed the data using Statistical Analysis System (SAS) (version 9.4; SAS Institute Inc., Cary, NC) and SUDAAN (version 13, Research Triangle Institute, Research Triangle Park, NC). Both SAS and SUDAAN incorporate sample weights (WTSB2YR) and design variables to account for unequal selection probabilities due to the complex, clustered design of NHANES and to account for the oversampling of certain groups. For concentrations below the LOD, we imputed a value equal to the LOD divided by the squared root of 2 [63]. To correct for urine dilution because of hydration differences in spot urine samples, as for

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other chemicals measured in NHANES urine samples [64], neonicotinoid biomarker concentrations (in micrograms of analyte per liter urine) were divided by the creatinine concentration (in grams creatinine per liter urine) and the results were reported as micrograms analyte per gram creatinine.

For the descriptive analyses, we stratified age, self-reported in years at the last birthday, in five groups: 3–5, 6–11, 12–19, 20–59, and ≥60 years. Based also on self-reported data we defined four race/ethnicity groups: non-Hispanic black, non-Hispanic white, all Hispanic, and Other. For some analyses, we categorized race/ethnicity as Asian vs non-Asian; also, based on the month of the physical examination at the MEC, we categorized season of the year as winter (Nov 1–Apr 30) or summer (May 1–Oct 31). We calculated distribution percentiles and mean concentrations in micrograms per liter [μg/L] and in micrograms per gram of creatinine [μg/g creatinine] using the survey sampling weights. We calculated geometric means only if the proportion of results below the LOD was greater than 40% [64]. We also evaluated the relationship between mean fasting time in hours (from self-reported information) and urinary metabolite concentrations by age group to determine whether food intake may contribute to exposure, as observed before for some phthalates, another class of environmental chemicals [65,66].

We calculated weighted Spearman correlations between samples with detectable concentrations of both the parent compound (acetamiprid or imidacloprid) and its corresponding metabolite (N-desmethyl-acetamiprid or 5-hydroxy-imidacloprid) without taking into account the complex survey sampling design. We used weighted univariate logistic regressions to examine the likelihood of having concentrations of the two metabolites (N-desmethyl-acetamiprid and 5-hydroxy-imidacloprid) above the 95^{th} percentile (a value we selected to represent the higher end of concentration distribution) when concentrations of their respective parent compounds were detectable.

Also, we conducted weighted multiple logistic regressions to examine the likelihood of concentrations being above the 95^{th} percentile for the two biomarkers detected most frequently (N-desmethyl-acetamiprid and 5-hydroxy-imidacloprid) based upon sex, age group (3–5, 6–11, 12–19, 20–59, ≥60 years old), race/ethnicity (Asian [N=305] vs non-Asian [N=2,733]), season (summer vs winter), fasting time (low [≤8 hour, N= 1,778] vs high [>8 hour, N=1,260]), and creatinine, variables selected on the basis of statistical, demographic, or biologic considerations.

For each analyte, to reach the final multivariate logistic regressions model, we used backward elimination including all the two-way interaction terms, with a threshold of $P < 0.05$ for retaining the variable in the model, using Satterwaite-adjusted F statistics. We evaluated for potential confounding by adding back into the model one by one each of the excluded variables and examining changes in the β coefficients of the statistically significant main effects. If addition of a variable changed a β coefficient by ≥ 10%, the variable was re-added to the model.

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3. Results

We quantified urinary concentrations of six neonicotinoid biomarkers in 3,038 NHANES 2015–2016 participants. The weighted detection frequencies were highest for N-desmethyl-acetamiprid (35%) and 5-hydroxy-imidacloprid (19.7%) (Tables 1–2), followed by clothianidin (7.7%), and imidacloprid (4.3%) (Tables S1–S2). Acetamiprid and thiacloprid (Tables S3–S4) were seldom detected (<0.5%). The weighted frequency of detecting at least one of the six neonicotinoids biomarkers was 49.1%.

In Tables 1–2, we also present select percentiles, and weighted detection frequencies stratified by age group, sex, and race/ethnicity for N-desmethyl-acetamiprid and 5-hydroxy-imidacloprid, and in Tables S1–S4 for the other analytes. Detection frequencies for N-desmethyl-acetamiprid, 5-hydroxy-imidacloprid and clothianidin were higher in the Other category than in the other race/ethnicity groups (Table 1, 2, S1). Because Asians accounted for 56.1% of participants in the Other category and were 5.5% of the total population sample, we chose to compare Asians to non-Asians for this part of the analysis. Also, because the proportion of results below the LOD was greater than 40% for all compounds examined, we did not calculate geometric means. The 95th percentiles for N-desmethyl-acetamiprid, 5-hydroxy imidacloprid, and clothianidin were 1.29, 1.37, and 0.396 μg/L, respectively (Tables 1–2, S1). The highest observed values were comparable for N-desmethyl-acetamiprid (34.7 μg/L), 5-hydroxy-imidacloprid (40.4 μg/L), and clothianidin (31.1 μg/L), and considerably lower for imidacloprid (4.94 μg/L), thiacloprid (1.79 μg/L), and acetamiprid (1.70 μg/L) (Tables 1–2, S1–S4).

Because of the relatively low detection of clothianidin, imidacloprid, acetamiprid and thiacloprid, only N-desmethyl-acetamiprid and 5-hydroxy-imidacloprid data were analyzed further. Weighted Spearman correlations coefficients between the concentrations of acetamiprid and N-desmethyl-acetamiprid and between imidacloprid and 5-hydroxy-imidacloprid were 0.337 and 0.453, respectively, among the samples with detectable concentrations of both parent compound and metabolite.

N-desmethyl-acetamiprid

Median and 95th concentrations (95% CI) of N-desmethyl-acetamiprid in the 2015–2016 NHANES population were <LOD and 1.29 (1.09-1.72) μg/L, respectively; median, select percentile concentrations and their 95% CI by age group (i.e., 3–5, 6–11, 12–19, 20–59, and 60+ years of age) are also provided in Table 1. Having a detectable concentration of acetamiprid was 1.89 times more likely when the concentration of its metabolite N-desmethyl-acetamiprid was above the 95th percentile (adjusted odds ratio [OR] = 1.89 (95% confidence interval [CI] = 0.32-15.30)).

Race, season, age group, fasting time, and age group×fasting time remained significant in the final model to identify significant factors associated with the odds of having concentrations of N-desmethyl-acetamiprid above the 95th percentile (Table 3). In a final model without including fasting time, age group, race (Asian vs non-Asian), and season remained significant (data not shown).

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Among people who fasted for <8h (fasting time low), 3–5 year old children were more likely to have N-desmethyl-acetamiprid concentrations above the 95th percentile than 12–19 year olds (adjusted OR = 3.12 (95% CI = 0.98-9.98)) and 20–59 year olds (4.29 (2.04-9)). Children 6–11 years of age were more likely than 20-59 year olds to have N-desmethyl-acetamiprid concentrations above the 95th percentile (2.65 (1.2-5.84)). Lastly, adults 60 years of age and older who fasted for <8 hours were more likely than young adults (20–59 years) to have N-desmethyl-acetamiprid concentrations above the 95th percentile (3.86 (2.06-7.25)).

For people fasting longer than 8 hours (fasting time high), children 3–5 years of age were more likely to have N-desmethyl-acetamiprid concentrations above the 95th percentile than 6–11 year olds (4.51 (1.19-17.05)), 12–19 year olds (7.18 (1.93-26.74)), 20–59 year olds (2.87 (1.19-6.92)), and adults ≥60 years (3.6 (1.12-11.59)).

Asians were almost two times more likely (1.94 (1.08-3.49)) than non-Asians to have concentrations above the 95th percentile of N-desmethyl-acetamiprid. Last, samples collected during the summer were 1.55 times more likely (95% CI=1.03-2.32)) to have N-desmethyl-acetamiprid concentrations above the 95th percentile than samples collected in winter.

5-hydroxy-imidacloprid

The median and 95th concentrations (95% CI) for 5-hydroxy-imidacloprid in the total 2015–2016 NHANES population were <LOD and 1.37 (1.04-1.99) μg/L, respectively (Table 2).

Detecting imidacloprid was 19.7 (10.63-36.43) times more likely when the concentration of its metabolite 5-hydroxy-imidacloprid was above the 95th percentile. After assessing the significant factors associated with the odds of having concentrations of 5-hydroxy-imidacloprid above the 95th percentile, which included age group, race, sex, season, creatinine, and fasting time, only season and race remained significant in the final model, and these are the only variables discussed further. Samples collected during the summer were more likely to have 5-hydroxy-imidacloprid concentrations above the 95th percentile than those collected in winter (adjusted OR = 2.43; 95% CI, (1.22-4.84) and Asians were more likely than non-Asians to have 5-hydroxy-imidacloprid concentrations above the 95th percentile (adjusted OR = 2.25; 95% CI, (1.44-3.51)).

4. Discussion

For the first time, we present nationally representative data for four neonicotinoids and two of their metabolites among the U.S. general population 3 years of age and older. Depending on the neonicotinoid biomarker, concentrations spanned 1–2 orders of magnitude. The most detected biomarkers were the two metabolites N-desmethyl-acetamiprid and 5-hydroxy-imidacloprid. Clothianidin and imidacloprid were detected in fewer than 10% of the population, while acetamiprid and thiacloprid were seldom detected (<0.5%). Almost 50% of the U.S. general population had detectable concentrations of at least one of the six neonicotinoids biomarkers, in agreement with common use of neonicotinoids in commerce. For example, acetamiprid containing products are registered for use in cotton, vegetables,

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potato, orchards, vines, citrus, tea and ornamentals, and for the control of termites and household pests [8]. Imidacloprid was the most widely used neonicotinoid insecticide in the USA for agricultural purposes during 2015 and 2016 with an estimated ca. 1 million pounds used per year, excluding seed treatment uses, with major uses being on soybeans, cotton, vegetables, and fruits [67]. Imidacloprid is also used in polystyrene insulation, vinyl siding, adhesives, sealants, textiles for outdoor uses, and pressure-treated wood decking [24]. These uses suggest potential neonicotinoid exposure.

In this study, we detected the imidacloprid and acetamiprid metabolites, 5-hydroxy-imidacloprid and N-desmethyl-acetamiprid, more frequently than their corresponding parent compounds suggesting that the metabolites may provide a better way for assessing background exposures. Of note, exposure to the metabolites themselves may also occur because neonicotinoids may convert to their metabolites in the environment; much like the presence of dialkylphosphates, environmental degradation products of organophosphate insecticides, in the body may result from exposure to the dialkyphosphates and not their parent compounds [68,69]. There is strong evidence that soils, waterways, and plants are contaminated or contain variable levels of neonicotinoids and their metabolites [70], some of which are the same as those in mammals [71]. Therefore, concentrations of neonicotinoid metabolites in urine may reflect both exposure to the parent compound or the environmental degradation products, some of which may also display mammalian in-vitro toxicity [72].

Spearman correlations between the concentrations of parent and corresponding metabolite, when both were detected, suggested weak (acetamiprid and N-desmethyl-acetamiprid) and moderate (imidacloprid and 5-hydroxy-imidacloprid) correlations. However, because of the relatively low detection frequency and concentrations, the parent compounds might not be suitable biomarkers of background exposure. As a result, the parent compounds would only be detectable after relatively high exposures (e.g., those expected to result in concentrations of the corresponding metabolite above the 95th percentile).

Although human metabolism studies are not available, in rats, the main metabolic pathway for acetamiprid is demethylation to produce N-desmethyl-acetamiprid. In contrast, imidacloprid metabolism includes several pathways and 5-hydroxy-imidacloprid is only one of the many possible metabolites [33]. Additionally, the LOD for 5-hydroxy-imidacloprid was two times higher than that of N-desmethyl-acetamiprid. Together, these facts could explain why N-desmethyl-acetamiprid was the most frequently detected neonicotinoid biomarker in the current study population.

There are no large population studies conducted in the United States or elsewhere on neonicotinoids biomonitoring. In a recent report on 10 children from Hangzhou, China [73], acetamiprid and imidacloprid were the most frequently detected neonicotinoids (80%), clothianidin was detected in 20% and thiacloprid in 10% of the samples collected. The method limits of quantification were 0.2 μg/L (imidacloprid, clothianidin, thiacloprid) and 0.1 μg/L (acetamiprid). This method did not include any metabolites. Investigators in Japan [74] measured seven neonicotinoids in the urine of 223 children 3 years of age and detected acetamiprid in 12.1% of the children‘s urine tested (LOD = 0.03 μg/L), imidacloprid in 15.2% (LOD = 0.31 μg/L), clothianidin in 8.1% (LOD = 1.07 μg/L) and thiacloprid in 0%

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(LOD = 0.32 μg/L). The authors did not quantify any neonicotinoid metabolites, only parent compounds and reported that the sum of all neonicotinoids measured was significantly higher in summer than in winter, which agrees with our findings. People may consume more fresh fruits and vegetables in the summer, compared to winter. Furthermore, pests are more abundant with higher temperatures [75], and higher pesticide amounts might be needed to protect crops, which could also contribute to higher urinary concentrations of neonicotinoid biomarkers during warmer months. A separate study [76] identified four neonicotinoids including imidacloprid, acetamiprid, and N-desmethyl-acetamiprid which were quantified in five out of 36 urine samples collected from pregnant women living in agricultural areas of Almeria, Spain. Imidacloprid was identified in one sample at 1.57 μg/L. Both acetamiprid and N-desmethyl-acetamiprid were detected in one sample at 0.44 and 1.00 μg/L, respectively. N-desmethyl-acetamiprid was identified in three urine samples at 0.23, 0.94 and 1.03 μg/L. These concentrations are below the highest values observed in the 2015–2016 NHANES.

Children 3–5 years of age had higher concentrations of N-desmethyl acetamiprid than any other age groups. These concentrations were about two times higher than those in the corresponding percentile of the total population, suggesting that exposures can occur at young ages. However, reasons for such concentration differences by age are unclear.

Diet is likely to be a major route of exposure. In 2015–2016, acetamiprid was detected in more than 20% of nectarines, 60% of cherries and apple sauce, and in about 30% of apples and strawberries [77,78], common food staples in children's diets, suggesting a potential dietary contribution to exposure. Of interest, for other dietary contaminants such as some phthalates [66,65], fasting times were inversely associated with biomarkers concentrations. However, in this study, fasting time did not influence having concentrations of 5-hydroxy-imidacloprid above the 95th. Of note, regardless of fasting time, only children 3–5 years of age were more likely than adults to have N-desmethyl-acetamiprid concentrations above the 95th percentile, which suggests that factors other than diet might contribute to exposure in young children. For example, acetamiprid has become common in household pest control [79–83], and children could be exposed to neonicotinoids while playing with pets. Also, imidacloprid was detected in household dust in Italy [25], suggesting dust as a possible exposure source to neonicotinoids, especially considering children's playing behaviors. Unfortunately, we are unaware of studies reporting neonicotinoids data on paired house dust and urine samples, and the 2015–2016 NHANES did not collect information on pet ownership. Nevertheless, the potential effect of fasting and fasting time on urinary neonicotinoid biomarker concentrations merits future investigation.

We speculate that the higher likelihood of Asians having concentrations above the 95th percentile of 5-hydroxy-imidacloprid and N-desmethyl-acetamiprid than non-Asians may relate to Asians' relatively high consumption of tea and soybean-related products. Tea and soy foods may represent a potential source of human exposure to neonicotinoids because of the use of these insecticides in tea cultivation [48,49,84] and the high percentage (44-50%) of soybean seeds planted in the USA being treated with neonicotinoids. However, a recent study in Japan involving 373 adults did not find a significant correlation between neonicotinoid measurements in urine and tea intake [85].

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5. Conclusion

In this first nationally representative assessment of exposure to several neonicotinoids, we found that 49.1% of the U.S. general population 3 years of age and older had been recently exposed to neonicotinoids. The data also suggest metabolites are better biomarkers of background exposure than the compounds themselves. Research is needed to identify additional biomarkers of exposure to neonicotinoids and to evaluate changes in neonicotinoid exposure over time. Further studies to assess dietary intake of neonicotinoids and their metabolites, including consumption of organic vs conventional produce, the effects of fasting status and fasting time, as well as the relationship between neonicotinoid biomarkers and neonicotinoid dust measurements, pet ownership and pet neonicotinoid treatments, will be useful for a better understanding of neonicotinoid exposure sources. .

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Geometric mean and selected percentiles of N-desmethyl-acetamiprid concentrations in urine (first row in μg/L, shaded row in μg/g creatinine) for the U.S. population ≥3 years of age. Data from the National Health and Nutrition Examination Survey 2015-2016.

	Geometric mean (95% CI)	Selected percentile (95% CI)				Sample size	Weighted detection frequency
		50th	75th	90th	95th		
Total	*	< LOD	.331 (.272-.385)	.797 (.640-.956)	1.29 (1.09-1.72)	3012	35
	*	< LOD	.438 (.378-.488)	1.06 (.795-1.30)	1.93 (1.55-2.38)	3011	
Age group							
3-5 years	*	.202 (<LOD-.238)	.707 (.533-.834)	1.50 (1.13-2.35)	2.57 (1.52-3.70)	503	50.5
	*	.636 (<LOD-.737)	1.48 (1.16-1.95)	3.65 (2.52-4.59)	5.38 (4.30-6.10)	502	
6-11 years	*	< LOD	.480 (.331-.662)	1.01 (.786-1.59)	1.62 (.981-2.23)	416	46.7
	*	< LOD	.667 (.518-.848)	1.42 (1.00-2.38)	2.73 (1.69-3.80)	416	
12-19 years	*	< LOD	.380 (.265-.472)	.742 (.527-.956)	.998 (.742-1.69)	403	37.8
	*	< LOD	.321 (.237-.457)	.665 (.483-1.15)	1.24 (.652-2.23)	403	
20-59 years	*	< LOD	.298 (.211-.373)	.714 (.544-.963)	1.24 (.923-1.60)	1144	32.2
	*	< LOD	.372 (.311-.467)	.856 (.609-1.28)	1.56 (1.08-2.09)	1144	
60 years and older	*	< LOD	.312 (.246-.376)	.648 (.475-1.08)	1.87 (.986-2.42)	546	33.8
	*	< LOD	.424 (.341-.551)	1.02 (.816-1.35)	2.49 (1.20-4.75)	546	
Gender							
Males	*	< LOD	.285 (.211-.376)	.640 (.498-.923)	1.16 (.903-1.85)	1491	31.8
	*	< LOD	.318 (.275-.378)	.700 (.584-.900)	1.24 (.963-1.55)	1491	
Females	*	< LOD	.361 (.297-.450)	.934 (.760-1.00)	1.36 (1.16-1.86)	1521	38
	*	< LOD	.538 (.438-.667)	1.40 (1.00-1.90)	2.22 (1.88-3.26)	1520	

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	Geometric mean (95% CI)	Selected percentile (95% CI)				Sample size	Weighted detection frequency
		50th	75th	90th	95th		
Race/ethnicity							
All Hispanic	*	< LOD	.310 (.251-.376)	.674 (.550-.866)	1.16 (.882-1.60)	980	35.8
	*	< LOD	.424 (.368-.470)	.963 (.737-1.17)	1.56 (1.29-2.33)	980	
Non-Hispanic Blacks	*	< LOD	.323 (.260-.361)	.787 (.611-.945)	1.67 (1.07-2.11)	707	33.7
	*	< LOD	.311 (.263-.378)	.779 (.648-1.00)	1.35 (1.12-1.99)	706	
Non-Hispanic Whites	*	< LOD	.309 (.246-.385)	.752 (.568-.976)	1.28 (.986-1.87)	876	33.6
	*	< LOD	.439 (.350-.500)	1.08 (.710-1.60)	2.00 (1.56-2.84)	876	
Others	*	< LOD	.517 (.373-.714)	1.08 (.935-1.24)	1.52 (1.16-1.98)	449	43.3
	*	< LOD	.560 (.431-.700)	1.27 (.881-1.67)	1.93 (1.40-2.94)	449	

CI, confidence interval; LOD, limit of detection

< LOD means less than the limit of detection of 0.2 μg/L.

The weighted detection frequency represents the detection percentage of the population.

*Not calculated. Proportion of results below the limit of detection was too high to provide a valid result.

Sample size may differ because of missing laboratory results.

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Table 2.

Geometric mean and selected percentiles of 5-hydroxy-imidacloprid concentrations in urine (first row in μg/L, shaded row in μg/g creatinine) for the U.S. population ≥3 years of age. Data from the National Health and Nutrition Examination Survey 2015-2016.

	Geometric mean (95% CI)	Selected percentile (95% CI)				Sample size	Weighted detection frequency
		50th	75th	90th	95th		
Total	*	< LOD	< LOD	.872 (.719-.936)	1.37 (1.04-1.99)	2878	19.7
	*	< LOD	< LOD	1.27 (1.08-1.44)	1.85 (1.58-2.15)	2877	
Age group							
3-5 years	*	< LOD	< LOD	.819 (.446-1.12)	1.14 (.715-2.17)	486	17.3
	*	< LOD	< LOD	2.48 (1.87-3.03)	3.65 (2.80-4.89)	485	
6-11 years	*	< LOD	< LOD	.970 (.630-1.18)	1.38 (1.04-2.14)	404	16.5
	*	< LOD	< LOD	1.51 (1.22-1.82)	2.41 (1.82-2.80)	404	
12-19 years	*	< LOD	< LOD	.834 (.483-1.04)	1.03 (.760-3.38)	390	19.6
	*	< LOD	< LOD	.757 (.582-1.33)	1.44 (.757-1.78)	390	
20-59 years	*	< LOD	< LOD	.908 (.705-1.11)	1.53 (1.03-2.50)	1078	21.2
	*	< LOD	< LOD	1.25 (.991-1.66)	2.03 (1.40-2.84)	1078	
60 years and older	*	< LOD	< LOD	.719 (.522-.997)	1.15 (.808-1.61)	520	17.3
	*	< LOD	< LOD	1.15 (.924-1.33)	1.52 (1.16-1.75)	520	
Gender							
Males	*	< LOD	< LOD	.858 (.650-1.08)	1.35 (.970-2.50)	1415	20.8
	*	< LOD	< LOD	1.06 (.902-1.27)	1.54 (1.16-1.87)	1415	
Females	*	< LOD	< LOD	.872 (.685-.954)	1.38 (.978-1.97)	1463	18.6
	*	< LOD	< LOD	1.47 (1.27-1.68)	2.33 (1.68-2.99)	1462	

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	Geometric mean (95% CI)	Selected percentile (95% CI)				Sample size	Weighted detection frequency
		50th	75th	90th	95th		
Race/ethnicity							
All Hispanic	*	< LOD	< LOD	.753 (.586-.936)	1.17 (.934-1.43)	944	17.4
	*	< LOD	< LOD	1.19 (1.00-1.28)	1.66 (1.40-2.00)	944	
Non-Hispanic Blacks	*	< LOD	< LOD	.848 (.628-1.03)	1.25 (.936-1.48)	681	19.8
	*	< LOD	< LOD	.881 (.781-1.04)	1.23 (1.12-1.51)	680	
Non-Hispanic Whites	*	< LOD	< LOD	.885 (.658-1.09)	1.61 (.922-2.73)	837	19.4
	*	< LOD	< LOD	1.38 (1.08-1.72)	2.03 (1.58-2.83)	837	
Others	*	< LOD	.401 (<LOD-.577)	.880 (.727-1.16)	1.43 (1.11-2.54)	416	25.3
	*	< LOD	.778 (<LOD-.959)	1.19 (1.12-1.40)	1.61 (1.39-2.42)	416	

CI, confidence interval; LOD, limit of detection

< LOD means less than the limit of detection of 0.4 μg/L.

The weighted detection frequency represents the detection percentage of the population.

*Not calculated. Proportion of results below the limit of detection was too high to provide a valid result.

Sample size may differ because of missing laboratory results.

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Table 3.

Adjusted[a] odds ratio for having N-desmethyl-acetamiprid concentrations above the 95th percentile by fasting time, age group, season, and race. Bold font indicates $p < 0.05$

Comparison	Adjusted OR	Lower 95% Limit	Upper 95% Limit
fasting time low, 3-5 vs 6-11	1.62	0.67	3.92
fasting time low, 3-5 vs 12-19	3.12	0.98	9.98
fasting time low, 3-5 vs 20-59	**4.29**	**2.04**	**9**
fasting time low, 3-5 vs 60+	1.11	0.49	2.5
fasting time low, 6-11 vs 12-19	1.93	0.7	5.32
fasting time low, 6-11 vs 20-59	**2.65**	**1.2**	**5.84**
fasting time low, 12-19 vs 20-59	1.37	0.46	4.1
fasting time low, 60 vs 6-11	1.46	0.7	3.05
fasting time low, 60 vs 12-19	2.81	0.87	9.12
fasting time low, 60 vs 20-59	**3.86**	**2.06**	**7.25**
fasting time high, 3-5 vs 6-11	**4.51**	**1.19**	**17.05**
fasting time high, 3-5 vs 12-19	**7.18**	**1.93**	**26.74**
fasting time high, 3-5 vs 20-59	**2.87**	**1.19**	**6.92**
fasting time high, 3-5 vs 60+	**3.6**	**1.12**	**11.59**
fasting time high, 6-11 vs 12-19	1.59	0.19	13.5
fasting time high, 20-59 vs 6-11	1.57	0.6	4.14
fasting time high, 20-59 vs 12-19	2.51	0.42	14.86
fasting time high, 20- 59 vs 60+	1.26	0.44	3.57
fasting time high, 60 vs 6-11	1.25	0.45	3.49
fasting time high, 60 vs 12-19	2	0.44	9.11
Age 3-5 : fasting time low vs high	0.9	0.39	2.04
Age 6-11 : fasting time low vs high	2.49	0.9	6.86
Age 12-19 : fasting time low vs high	2.06	0.36	11.94
Age 20-59 : fasting time low vs high	0.6	0.3	1.2
Age 60+ : fasting time low vs high	2.9	0.93	9.01
Summer vs Winter	**1.55**	**1.03**	**2.32**
Asian vs Non-Asian	**1.94**	**1.08**	**3.49**

[a]Adjusted with sex, age group (3–5, 6–11, 12–19, 20–59, ≥60 years old), race/ethnicity (Asian vs Non-Asian), season (summer vs winter), fasting time (low [≤8 hour] vs high [>8 hour]), and creatinine. Confidence intervals that include 1 represent non-significant findings.