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# Characterization of Daily Dietary Intake and the Health Risk of Neonicotinoid Insecticides for the U.S. Population

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**ABSTRACT:** Although neonicotinoids have been the most commonly used insecticides globally, very limited data related to their dietary intake and health risks are available. In this study, we used the relative potency factor approach to aggregate individual neonicotinoids into a single metric ($IMI_{RPF}$) representing the intakes of total neonicotinoids in relation to imidacloprid for each food item. We then estimated the average daily intake (ADI) of neonicotinoids using residue data collected from U.S. Congressional Cafeteria study (USCC) and USDA/PDP and food consumption data from NHANES 2011−2012. Among the USCC and USDA/PDP samples, squash (427.2 ng/g) and spinach (569.2 ng/g), had the highest average $IMI_{RPF}$, respectively. The estimated ADIs were below the current chronic reference dose (cRfD) for imidacloprid. However, due to their wide use, it is logical to expect the ubiquity of neonicotinoids in foods. Therefore, the importance of conducting routine dietary intake assessment for neonicotinoids should not be ignored.

**KEYWORDS:** *neonicotinoids, daily dietary intake, dietary risk assessment, relative potency factor, average daily intake, imidacloprid, reference dose*



## INTRODUCTION

Neonicotinoids (neonics) are a group of systemic insecticides that includes acetamiprid, clothianidin, dinotefuran, imidacloprid, nitenpyram, thiacloprid, and thiamethoxam. The nature of their systemic property leads to universal translocation of neonics to tissues of the applied plants regardless of the application methods.[1] As a result, neonics protect the whole plant from insect damage by distributing the active ingredients to all tissues of the plant, including the edible components. Neonics have gradually become the most commonly used insecticides around the world since their introduction in the late 1990s. They accounted for approximately 24% and 27% of the global insecticide market in 2008 and 2010, respectively, with expected continuous growth of uses.[2,3] The invention and adoption of neonics in the 1990s were due to insects' resistance to the dominant classes of pesticides of carbamates, organophosphates, and pyrethroids used at that time.[1,4] In addition, the application of neonics in the seed treatment technology has led to the large-scale and rapid increase uses in field crops (e.g., soybeans and maize).[5] Two neonic compounds are in particularly wide use; including imidacloprid and thiamethoxam, which are registered for use on 140 and 115 crops worldwide and accounted for about 41.5% and 23.8% of the neonics sales in 2009, respectively.[3]

Previous and current research on neonics mainly focuses on their toxicological effects in invertebrates. The known mode of action of neonics, which is similar to nicotine, is to function as agonists on the nicotinic acetylcholine receptors (nAChRs).[1,2,6] Although insect's nAChR has a cationic subunit that can interact with the nitro- or cyano-end of neonics with higher affinity, mammalian nAChR does not.[1,2,6] Therefore, neonics are generally considered less toxic in humans than the cholinesterase inhibiting insecticides, such as carbamates or organophosphates, and thus very few studies were conducted on quantifying human exposure to neonics, not to mention the characterization of the potential adverse health effects.[7]

In this study, we demonstrated a model simulation methodology that allows not only for estimating population-base daily dietary intakes as the results of fruits and vegetables consumption but also for characterizing health risk of neonics by comparing the estimated total neonic dietary exposure distributions with the current chronic reference dose (cRfD) for imidacloprid.[3] Because of the frequent detection of multiple neonic compounds in the same fruit/vegetable items, we incorporated the relative potency factor approach[8,9] in this methodology in which will lead to a more representative risk assessment paradigm for total dietary intakes of neonics. The outcomes from this analysis shall improve future epidemiological investigation. Figure 1 details the approach taken for this study.

## MATERIALS AND METHODS

**Neonics Residues in Foods.** We measured residues of seven neonicotinoids in fruits and vegetables collected from the U.S. Congressional cafeteria (USCC study)[10] and obtained data published by the U.S. Department of Agriculture (USDA), Pesticide Data Program (PDP).[11−14] We supplemented residue data from the USCC study to expand the types of fruit and vegetable items that are reported by the USDA/PDP in order to better reflect potential exposures to neonics in foods consumed by people participated in the National Health and Nutrition Examination Survey (NHANES).

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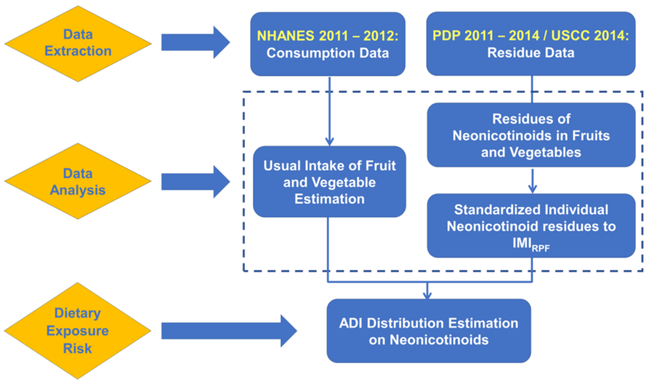


**Figure 1.** Schematic display of the research design.

For the USCC residue data, a total of 64 samples including seven fruits (apple, cantaloupe, cranberry, grapes, honeydew, melon, and strawberry) and seven vegetables (broccoli, cilantro, corn, cucumber, lettuce, pepper, spinach, and tomato) were analyzed for seven neonics (acetamiprid, clothianidin, dinotefuran, imidacloprid, nitenpyram, thiacloprid, and thiamethoxam) and flonicamid in 2014.[10] Flonicamid and nitenpyram were excluded from the model simulation due to the uncertain classification as a neonic and the lack of residue data, respectively. For the USDA/PDP data set, we extracted six neonics (no nitenpyram) from a total of 39 159 samples including 22 fruits and 29 vegetables (Table 1). USDA/PDP was initiated in early 1990s to measure pesticide residues in foods and to support U.S. Environmental Protection Agency (EPA)'s review of the maximum residue limits or tolerances for dietary exposure assessment. Fruit and vegetable samples were collected at volunteered terminal markets and large chain store distribution centers (approximately 2400 sites granted access and provided information in 2011 to 2014). PDP's operation procedures were developed to ensure that the samples are randomly selected from the national food distribution system to reflect what is typically available to the consumers while also with an emphasis on foods consumed by infants and children. The same commodities were cycled through PDP approximately every 5 years.[11−14]

**Residue Analysis.** The limits of detection (LODs) for individual neonic analyzed by the USCC study and USDA/PDP were listed in Table 1. All nondetectable (ND) residue concentrations were substituted with one-half of the LOD for model simulation purpose.[15]

We used the relative potency factor (RPF) approach[8,9] to integrate six neonics that are present in the same vegetable or fruit sample into a single measurement of imidacloprid$_{RPF}$ (IMI$_{RPF}$)[16,17] by using the respective chronic reference dose (cRfD), as shown in Table 1. As we adopted cRfD as the comparison metric of relative toxicity of neonics, this approach was also equivalent to the integration of comparing the margin of each neonic exposure to the corresponding cRfD. We chose imidacloprid as the reference neonic because it is the most widely used and studied neonic among all for risk communication purpose. Specifically, we used the following equation to calculate IMI$_{RPF}$ (the imidacloprid-equivalent total neonic) for each fruit or vegetable sample:

$$\mathrm{IMI_{RPF}} = \sum_k \mathrm{RPF}_k \times \mathrm{neonic}_k(\mathrm{ng/g})$$

where $k$ represents the specific neonics.

**Dietary Consumption Data.** We used fruit and vegetable consumption data collected by the Centers for Disease Control and Prevention (CDC), National Health and Nutrition Examination Survey (NHANES) 2011−2012, which was the latest publicly available data set online when we conducted this study in 2016. NHANES is designed to examine the health and nutritional status of the U.S. population excluding those residing in nursing homes, members of armed force, institutionalized persons, or U.S. nationals living abroad. In total, NHANES 2011−2012 obtained dietary recall information from 8519 individuals, 7605 of whom completed both days of the two 24-h dietary recall surveys. We included those 7605 participants in our usual intake (UI) analyses based on the NHANES sampling weights and the scope of data analyses.

**Long-Term Usual Consumption of Fruits and Vegetables.** In order to select nationally representative participants, NHANES uses a multistage probability sampling design in which each participant in the NHANES is weighted differently according to the sampling process as well as the questionnaires or biological examination provided. NHANES assigns a sample weight to each participant which represents the number of people in the population represented by such participant in NHANES, reflecting the unequal probability of selection, nonresponse adjustment, or adjustment to independent population controls. These weights were calculated from the base weight adjusting for nonresponse and poststratification adjusting to the 2000 U.S. Census population totals. We used WTDR2D for analyses on both days 1 and 2 dietary data. This two-day weight was constructed for the 7605 participants by taking the day 1 weights (WTDRD1) and further adjusting for (a) the additional nonresponse

**Table 1. Relative Potency Factors (RPF) for Neonicotinoids Based on Relative Chronic Reference Doses (cRfD)**

| neonicotinoid | NOAEL[a] (mg/kg/d) | study and observation end points | species | cRfD[b] (mg/kg/d) | RPF[c] | LOD[d] (ng/g) PDP | LOD[d] (ng/g) USCC | ref |
|---|---|---|---|---|---|---|---|---|
| acetamiprid (U.S. EPA 2012) | 7.1 | chronic/oncogenicity: decreased body weight and body weight gains in females and hepatocellular vacuolation in males. | rat | 0.071 | 0.8 | 1−160 | 0.03 | 31 |
| clothianidin (U.S. EPA 2005) | 9.8 | 2-generation reproduction: reduction in mean body weight gain; delayed sexual maturation; decreased absolute thymus weights in the first filial generation ($F_1$) pups. Increase in stillbirths in both generations | rat | 0.0098[e] | 5.8 | 1.5−90 | 0.03−0.15 | 32 |
| dinotefuran (U.S. EPA 2005) | 20[f] | chronic: decreased thymus weight in males | dog | 0.02[e] | 2.9 | 3−100 | 0.03−0.15 | 33 |
| imidacloprid (U.S. EPA 2005) | 5.7 | chronic/carcinogenicity: increased incidence of mineralized particles in thyroid colloid in males. | rat | 0.057 | 1.0 | 1−56 | 0.03−0.15 | 34 |
| thiacloprid (U.S. EPA 2003) | 1.2 | chronic: hepatic hypertrophy and cytoplasmic change and thyroid hypertrophy and retinal degeneration. | rat | 0.004[e] | 14.2 | 1−10 | 0.03 | 35 |
| thiamethoxam (U.S. EPA 2000) | 0.6 | 2-generation reproduction: Increased incidence and severity of tubular atrophy in testes of $F_1$ generation males. | rat | 0.006 | 9.5 | 1−80 | 0.03 | 36 |

[a]NOAEL, no observed adverse effect level. [b]cRfD, U.S. EPA derived chronic reference dose. [c]RPF, relative potency factor calculated based on cRfD of each neonic normalized by the cRfD of imidacloprid. [d]LOD, limit of detection. [e]Clothianidin: Additional 10× for the absence of developmental immunotoxicity study; Dinotefuran: Additional 10× for the extrapolation from LOAEL to NOAEL; Thiacloprid: Additional 3× as safety factor (SF) for the lack of morphometric assessments for the low- and mid-dose group animals in the developmental neurotoxicity study. [f]LOAEL, lowest observed adverse effect level.


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for the second recall and (b) for the proportion of weekend-weekday combinations of days 1 and 2 recalls.

We used SAS 9.4 in the application of the validated National Cancer Institute (NCI) method[18,19] to estimate the long-term usual intake (UI), which is defined as the long-term average daily consumption (g/day) in the NCI method. In addition, consumption data is usually right-skewed rather than symmetric since values can never be negative. Therefore, we log-transformed the two 24-h recalls approximating a normal distribution in order to estimate long-term usual consumption of fruit and vegetables by using the NCI method,[18,19] including both the probability of consuming a specific food item and the amount (gram) of such consumption in a day. In brief, NCI method fits the following two-part model with random mixed-effects for each vegetable/fruit item:

$$\text{logit}(p_{ij}) = \beta_0 + u_i$$

$$\log(\text{amount}_{ij}) = \beta_0^* + u_i^* + e_{ij}^* \quad e_{ij}^* \sim N(0, \sigma_{e*}^2)$$

$$\text{UI}_f(\text{g/day}) = p_f \times \text{amount}_f \quad f \text{ for individual food item}$$

$\beta_0$ and $\beta_0$* are the global intercepts for probability and amount models, respectively. $u_i$ and $u_i$* are the person-specific random effects and $e_{ij}$* is the within-person variations in the two 24-h recalls under the two-part model. Both models are fit using the NCI-established SAS macro, MIXTRAN, which outputs the parameter estimates for both the probability and the amount models. The DISTRIB macro used the results from the MIXTRAN macro to estimate the usual food intakes to calculate percentiles and cut points of the usual intake distribution. We used R statistical software (3.2.4) for all other analyses.

**Average Daily Intake (ADI) Estimation of Imidacloprid-Equivalent Total Neonic ($IMI_{RPF}$).** To capture how the residue levels of each food item, as well as how the dietary consumption would contribute to the overall ADI distribution, we performed the following steps.

*Residue.* We randomly sampled 1000 $IMI_{RPF}$ with replacement from both USCC and PDP residue data sets to estimate the corresponding fifth, median, and 95th percentile of the residues for each food item.

*Consumption.* To improve the precision of the estimated UI distributions, we used the DISTRIB macro to simulate 100 pseudopersons' UI of each food item for the 7605 NHANES participants with different simulated person-specific effects.

*ADI Estimation.* We combined the residue and consumption data sets by each food item for every NHANES participants. We then calculated the cumulative distribution of $IMI_{RPF}$ estimated ADI, using the following equation, based upon the individual participant's weights (WTDR2D) under different residue levels (5th and 95th percentile and mean).

$$\text{ADI(ng/kg/day)} = \sum_f \text{IMI}_{\text{RPF\_f}}(\text{ng/g}) \times \text{UI}_f(\text{g/day}) \\ \text{exposure duration(year)/BW(kg)} \\ \times \text{average lifetime(year)}$$

Specifically, f is an individual fruit or vegetable item, $UI_f$ is the long-term usual intake of the specific food item f, and BW is each participant's body weight (if missing, we used the average body weight of the participants who have the same characteristics, household income levels, gender, age groups, race and ethnicity, and adult education attainment as the body weight of such participant). The exposure duration is approximately the same as the average lifetime since the interest of exposure is for daily dietary consumption.

**Sensitivity Analysis.** We conducted sensitivity analyses on commonly sampled fruit and vegetable items in order to determine the magnitude of uncertainty of results originated from

The management of ND data: We have considered different methods to manage the ND data in which some were similar to method used by MacIntosh et al. (1996).[15] Rather than the original treatment (replacing ND with one-half of the LOD), we also replaced all ND values with 0, or random variables sampled from a uniform distribution ranging from 0 to the given LOD of the respective analytical method.

The inclusion of samples without repeated residue measurements. For instance, squash in the USCC study was not included in the data analysis due to the lack of repeated samples to capture its distribution.

## RESULTS AND DISCUSSION

For the 64 vegetable and fruit samples that the USCC study analyzed, the overall frequency of detection for at least one neonic (not including nitenpyram) was 91%. Thiamethoxam was the most frequently detected neonic (61%), followed by imidacloprid (58%), clothianidin (36%), acetamiprid (33%), dinotefuran (27%), and thiacloprid (6%). Among all analyzed food items, tomatoes contained the highest average level of clothianidin (9.1 ng/g), dinotefuran (18.9 ng/g), and imidacloprid (8.3 ng/g). Apples contained the highest average level of acetamiprid (19.1 ng/g), squash contained the highest level of thiamethoxam (43.1 ng/g), and peppers contained the highest level of thiacloprid (0.2 ng/g). Table 1 shows the calculated RPFs for neonics using the relative toxicity of individual neonics to that of imidacloprid. Overall, squash (with only one sample) had the highest average of $IMI_{RPF}$ (427.2 ng/g), followed by tomatoes (132.5 ng/g), peppers (88.30 ng/g), and honeydews (54.9 ng/g).

For the 36 167 fruit and vegetable samples that we extracted from USDA/PDP 2011 to 2014 data sets, the overall detection rate of at least one neonic was 15%, which is substantially lower than that of the USCC study. Cherries were most frequently detected with neonics (94%), followed by apples (59%), strawberries (47%), and peppers (47%). Imidacloprid was the most frequently detected neonic (7%) among those fruits and vegetables, followed by acetamiprid (5%), thiamethoxam (3%), dinotefuran (1%), and clothianidin (1%). Thiacloprid was the least frequently detected among the six neonics in both residue data sets. Hot peppers contained the highest average level of acetamiprid (40.3 ng/g) and dinotefuran (41.4 ng/g); onions contained the highest average level of clothianidin (23.3 ng/g) and thiamethoxam (20.4 ng/g); and cherries contained the highest average level of imidacloprid (32.1 ng/g) and thiacloprid (12.2 ng/g). Overall, spinach had the highest average $IMI_{RPF}$ (569.2 ng/g), followed by baby food peas (482.5 ng/g), cherries (401.8 ng/g), baby food carrots (378.2 ng/g), and hot peppers (362.6 ng/g).

Table 2 shows the summary estimates of long-term UI (g/day) using NHANES consumption 2011−2012 data, which are essential for model simulation of ADI estimation. For the USCC data set, we included seven out of 12 vegetables and all 6 fruits in the final analysis but excluded squash because of the lack of multiple residue measurements and edamame due to no consumption as reported by the NHANES participants in the two 24-h recalls. We also excluded cilantro, kale, and zucchini as the result of a SAS macro warning of unstable estimation because of rare consumption (less than 10 participants had two 24-h recall consumption). For the USDA/PDP data set, we included 22 out of 29 vegetable commodities and 17 out of 22 fruit commodities in the final analysis. We excluded cherry tomatoes, infant formula (soy-based), and soybean grain from all analyses because no NHANES participants consumed those items in the two 24-h recalls. Beets (canned), mushrooms, papaya, peaches (baby food), and raspberries (fresh and


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**Table 2. Descriptive Statistics of Estimated Long-Term Usual Intake (UI) from NHANES 2011−2012**

| | | long-term usual intake (g/day) | | | |
|---|---|---|---|---|---|
| | food items | mean | fifth | median | 95th |
| vegetables | avocado | 1.79 | 0.69 | 1.67 | 3.32 |
| | green beans[a,d] | 5.36 | 0.60 | 3.36 | 16.79 |
| | broccoli | 4.85 | 0.28 | 2.36 | 17.63 |
| | cabbage | 1.88 | 0.20 | 1.36 | 5.31 |
| | carrot[d] | 4.44 | 0.10 | 1.63 | 18.30 |
| | cauliflower | 1.17 | 0.35 | 1.02 | 2.50 |
| | celery | 1.04 | 0.09 | 0.64 | 3.31 |
| | corn[b] | 5.28 | 2.30 | 5.03 | 9.13 |
| | cucumber | 3.49 | 0.04. | 0.91 | 15.05 |
| | hot pepper | 0.06 | 0.04 | 0.06 | 0.09 |
| | lettuce | 10.84 | 1.31 | 7.34 | 32.14 |
| | onion | 2.31 | 0.15 | 1.23 | 8.13 |
| | snap peas[d] | 1.88 | 1.82 | 1.88 | 1.93 |
| | bell pepper | 2.10 | 0.09 | 0.91 | 7.97 |
| | spinach[a] | 2.31 | 0.02 | 0.49 | 10.10 |
| | squash[c] | 2.06 | 1.01 | 1.95 | 3.49 |
| | tomato | 11.93 | 0.73 | 7.12 | 39.47 |
| fruits | apples | 19.83 | 0.31 | 7.12 | 85.34 |
| | apple juice | 12.64 | 0.01 | 0.94 | 70.11 |
| | apple sauce[d] | 1.50 | 0.31 | 1.32 | 3.31 |
| | banana | 18.63 | 0.39 | 8.23 | 73.27 |
| | blueberries[e] | 1.91 | <0.01 | 0.14 | 9.50 |
| | cantaloupe | 3.86 | 0.44 | 2.42 | 11.99 |
| | cherries[f] | 1.70 | 1.65 | 1.70 | 1.75 |
| | cranberries | 0.46 | 0.04 | 0.25 | 1.52 |
| | grape juice | 3.49 | 1.14 | 2.96 | 7.63 |
| | grapes | 4.74 | 0.13 | 1.78 | 19.83 |
| | honeydew melon | 0.74 | 0.25 | 0.63 | 1.58 |
| | nectarine | 1.93 | 1.40 | 1.92 | 2.49 |
| | orange juice | 35.28 | 0.25 | 9.69 | 162.85 |
| | peach | 4.79 | 0.02 | 0.8 | 22.3 |
| | pear[d] | 0.05 | <0.01 | <0.01 | 0.02 |
| | plum | 0.70 | 0.26 | 0.61 | 1.45 |
| | strawberries | 3.86 | 0.06 | 1.09 | 17.17 |
| | tangerine | 1.36 | 0.60 | 1.24 | 2.55 |
| | watermelon | 9.12 | 8.73 | 9.12 | 9.53 |

[a]Including canned and frozen. [b]Sweet corns, including fresh and frozen. [c]Including summer and winter squash. [d]Including baby foods. [e]Including cultivated and frozen. [f]Including frozen.

frozen) were also excluded by the NCI method due to less than 10 participants reported consumptions of those items. Because of the right skewness of the usual intake (UI) distribution, we reported both mean and median of UIs for comparisons. Tomatoes (11.9 and 7.1 g/day) and lettuce (10.8 and 7.9 g/day) had the highest mean and median UI of vegetables, respectively, whereas orange juice (35.3 and 9.7 g/day) and bananas (18.6 and 8.2 g/day) had the highest mean and median UI among all fruits, respectively.

Table 3 shows the descriptive statistics of the estimated average daily intake (ADI) of imidacloprid-equivalent total neonics, or $IMI_{RPF,}$ under the assumption that the mean imidacloprid-equivalent total neonics was used as the neonic residue level in fruits and vegetables that were consumed. For items collected from the USCC study, tomatoes contributed the most to the ADI of $IMI_{RPF,}$ among vegetables at the fifth percentile (1.33 ng/kg/day), median (14.4 ng/kg/day), and the 95th percentile (108 ng/kg/day). Apples contributed the most to the ADI of $IMI_{RPF}$ among fruits at median (2.03 ng/kg/day) and the 95th percentile (28.6 ng/kg/day), whereas honeydews contributed the most of ADI at the fifth percentile (0.12 ng/kg/day). For USDA/PDP data set, squash, tomatoes,

**Table 3. Estimated Average Daily Intake (ADI) of Total Neonics As the Results of Fruit and Vegetable Consumption Using Average IMIRPF As the Neonic Residue[g]**

| | | ADI (ng/kg/day) | | | |
|---|---|---|---|---|---|
| | USCC food items | mean | fifth | median | 95th |
| vegetables ($N$ = 7) | broccoli | 0.34 | 0.01 | 0.13 | 1.25 |
| | corn | 0.01 | <0.01 | <0.01 | 0.02 |
| | cucumber | 0.67 | 0.01 | 0.14 | 2.70 |
| | lettuce | 0.36 | 0.03 | 0.19 | 1.20 |
| | pepper | 3.70 | 0.11 | 1.24 | 14.00 |
| | spinach | 1.45 | 0.01 | 0.24 | 5.90 |
| | tomato | 31.50 | 1.33 | 14.40 | 108.00 |
| fruits ($N$ = 6) | apple | 7.17 | 0.08 | 2.03 | 28.60 |
| | cantaloupe | 1.23 | 0.09 | 0.59 | 4.18 |
| | cranberries | 0.12 | 0.03 | 0.08 | 0.35 |
| | grapes | 0.10 | <0.01 | 0.03 | 0.42 |
| | honeydew | 0.57 | 0.12 | 0.36 | 1.72 |
| | strawberries | 1.27 | 0.01 | 0.28 | 5.28 |
| | PDP/USDA food items | mean | fifth | median | 95th |
| vegetables ($N$ = 16) | avocado | 2.12 | 0.51 | 1.42 | 6.38 |
| | green beans[a,d] | 11.19 | 0.84 | 5.36 | 38.14 |
| | broccoli | 15.80 | 0.62 | 5.95 | 58.60 |
| | cabbage | 2.95 | 0.22 | 1.60 | 9.57 |
| | carrot[d] | 6.43 | 0.11 | 1.84 | 25.50 |
| | cauliflower | 1.20 | 0.23 | 0.76 | 3.60 |
| | celery | 1.53 | 0.09 | 0.72 | 5.30 |
| | corn[b] | 7.63 | 2.01 | 5.16 | 23.02 |
| | hot pepper | 0.46 | 0.18 | 0.32 | 1.40 |
| | lettuce | 12.50 | 1.02 | 6.42 | 41.40 |
| | onion | 16.50 | 0.72 | 6.80 | 59.60 |
| | peas[d] | 2.00 | 0.86 | 1.37 | 6.16 |
| | pepper | 11.80 | 0.35 | 3.96 | 44.80 |
| | spinach[a] | 26.20 | 0.16 | 4.36 | 106.00 |
| | squash[c] | 9.30 | 2.69 | 6.27 | 28.02 |
| | tomato | 15.90 | 0.67 | 7.28 | 54.70 |
| fruits ($N$ = 16) | apple juice | 15.10 | 0.01 | 0.88 | 72.10 |
| | apple | 31.60 | 0.35 | 8.85 | 126.00 |
| | applesauce[d] | 4.83 | 0.66 | 3.09 | 14.70 |
| | banana | 77.30 | 1.14 | 26.50 | 286.00 |
| | blueberries[e] | 5.07 | <0.01 | 0.29 | 22.13 |
| | cantaloupe | 14.10 | 1.08 | 6.75 | 48.00 |
| | cherries[f] | 13.70 | 5.91 | 9.38 | 42.20 |
| | grape juice | 4.05 | 0.82 | 2.53 | 12.20 |
| | nectarine | 10.40 | 4.04 | 7.17 | 31.80 |
| | orange juice | 35.50 | 0.18 | 7.63 | 149.00 |
| | peach | 16.50 | 0.06 | 2.12 | 70.10 |
| | pear[d] | 0.05 | <0.01 | <0.01 | 0.02 |
| | plum | 0.68 | 0.15 | 0.44 | 2.03 |
| | strawberries | 7.01 | 0.07 | 1.55 | 29.20 |
| | tangerine | 4.69 | 1.23 | 3.08 | 14.00 |
| | watermelon | 11.60 | 5.02 | 7.99 | 35.90 |

[a]Including canned and frozen. [b]Sweet corns, including fresh and frozen. [c]Including summer and winter squash. [d]Including baby foods. [e]Including cultivated and frozen. [f]Including frozen. [g]Common commodities collected in both residue data sets were colored in shade.


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and spinach contributed the most to the ADI of $IMI_{RPF}$ among vegetables at the fifth percentile (2.69 ng/kg/day), median (7.28 ng/kg/day), and at the 95th percentile (106 ng/kg/day), respectively. Cherries (5.91 ng/kg/day) and banana (26.5 and 286 ng/kg/day) contributed the most to the ADI of $IMI_{RPF}$ among fruits at the fifth and median and 95th percentile.

Figure 2 shows the estimated overall ADI distributions of $IMI_{RPF}$ via fruits and vegetables consumption using the USCC, USDA/PDP, and both data sets on the same scale of $IMI_{RPF}$ (*x*-axis), and its relationship to the cRfD of imidacloprid. Not surprisingly, the ADIs of $IMI_{RPF}$ were higher as the result of the combined fruits and vegetable consumption than only fruit or vegetable consumption for either USCC or USDA/PDP data sets. The ADIs of $IMI_{RPF}$ were higher using USDA/PDP data set than those using USCC data set regardless of the consumption items. Fruit consumption contributed more to the overall ADIs of $IMI_{RPF}$ than vegetables using USDA/PDP data set, whereas the ADIs of $IMI_{RPF}$ were higher via vegetable consumption than those via fruit consumption using the USCC data set. In general, we found that the estimations of ADI of $IMI_{RPF}$ using either residue data set were several orders of magnitude lower than the RfD of imidacloprid (57 000 ng/kg/d).

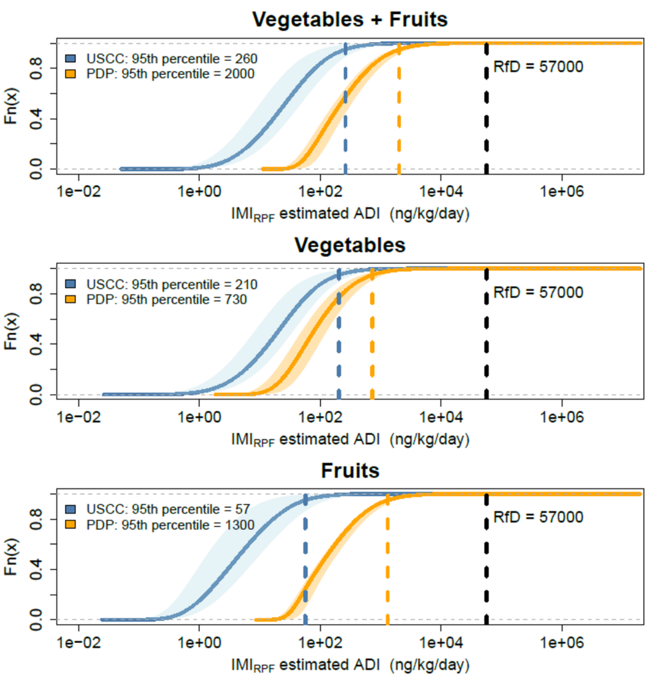


**Figure 2.** Average daily intake (ADI) distribution of neonicotinoids through fruit and vegetable consumption using USCC and PDP 2011−2014 data sets. The blue and orange shaded areas (fifth to 95th percentile of residue levels) and lines (median residue levels) showed the difference of cumulative density of $IMI_{RPF}$ estimated ADI originated from distribution of neonicotinoids residues in the USCC and PDP 2011−2014 data sets, respectively. The labeled 95th percentiles showed the 95th percentile $IMI_{RPF}$ estimated ADI when median residue levels in fruits and vegetables that are consumed.

Figure 3 shows the results from the sensitivity analyses for the estimations of ADI distributions by including fruits and vegetables (including broccoli, corn, lettuce, pepper, spinach, tomatoes, apple, cantaloupe, and strawberries) that were collected both by the USCC study and USDA/PDP 2011−2014. We summarized the ADI estimates with respect to different uncertainty scenarios and across different residue levels in Table 4. It appears that the results of ADI estimation using USCC residues were generally more stable than those using USDA/PDP residues. The estimated ADIs using the USCC study data were also relatively robust in terms of having similar means at different residue levels regardless of how those ND were managed, except for the inclusion of a single squash residue data. However, the estimations of ADI based on USDA/PDP residues were more variable across different ND management strategies. In the case that we replaced ND samples with zeros (Strategy #3 in Table 4), the USDA/PDP estimated ADIs were actually lower than those estimated by the USCC residue data when individuals consumed fruits and vegetables containing the fifth percentile and mean of $IMI_{RPF}$.

Because of the concern of a single large measurement of 427.2 ng/g of $IMI_{RPF}$, a value to which the ADI distributions could be significantly affected, we conducted additional sensitivity analyses by including squash as an uncertainty factor. We found large variations among squash's $IMI_{RPF}$, calculation in which the fifth and 95th percentiles of $IMI_{RPF}$ were 10 and 448.8 ng/g, respectively, using the USDA/PDP data set. Therefore, we have adopted the most conservative

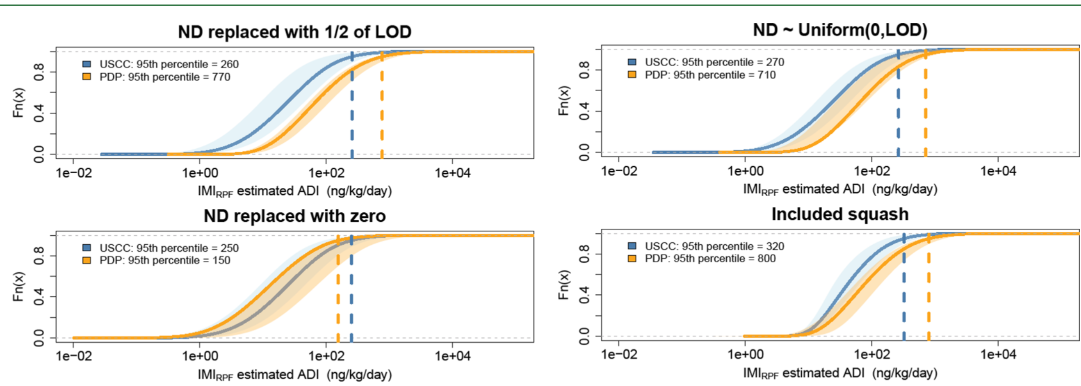


**Figure 3.** Results of the sensitivity analysis for both USCC and PDP 2011−2014 residue data sets. Only common vegetables and fruits, including broccoli, corn, lettuce, pepper, spinach, tomatoes, apple, cantaloupe, and strawberries in both data sets were included for comparison. The blue and orange shaded areas (fifth to 95th percentile of residue levels) and lines (median residue levels) showed the difference of cumulative density of $IMI_{RPF}$ estimated ADI originated from distribution of neonicotinoids residues in USCC and PDP 2011−2014, respectively. The labeled 95th percentiles showed the 95th percentile $IMI_{RPF}$ estimated ADI when median residue levels in fruits and vegetables that are consumed.


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**Table 4. Results from the Sensitivity Analysis on the Estimated Average Daily Intake (ng/kg/day) of Imidacloprid-Equivalent Total Neonics ($IMI_{RPF}$)**

| residue data set | uncertainty scenarios/ND management strategy[a] | estimated Mean ADI (p-value)[b] | | |
|---|---|---|---|---|
| | | 5th $IMI_{RPF}$ | mean $IMI_{RPF}$ | 95th $IMI_{RPF}$ |
| USCC | 1 | 26 | 66 | 122 |
| | 2 | 30* (<0.0001) | 69 | 124 |
| | 3 | 25 | 65 | 121 (0.78) |
| | 4 | 50* (<0.0001) | 91* (<0.0001) | 147* (<0.0001) |
| USDA/PDP | 1 | 163 | 202 | 338 |
| | 2 | 80* (<0.0001) | 189 | 259* (<0.0001) |
| | 3 | 0* (<0.0001) | 40* (<0.0001) | 217* (<0.0001) |
| | 4 | 165 | 215 | 372* (0.01) |

[a]ND management strategies: 1. NDs replaced with 1/2 of LODs; 2. NDs replaced with a random variable from Uniform (0, LOD); 3. NDs replaced with zero; Main analyses were conducted based on the shaded strategy; 4. Analyses included neonic residues from the single squash sample. Strategies 1−3 excluded neonic residues from the single squash sample. [b]Mean of the estimated ADI used the fifth, median, or 95th percentile residue levels of every common commodities included in the sensitivity analysis. P-values were for *t* tests comparing between strategies with Strategy #1. Bonferroni correction for the significance levels was used for multiple testing with p-values $<1.67 \times 10^{-2}$.

approach treating $IMI_{RPF}$ of USCC squash as a fixed value (427.2 ng/g) for all residue percentiles. We found that squash could be influential in terms of the relative percentage increase in the USCC ADI distributions involving mean $IMI_{RPF}$ residues. Compared to the original settings (strategy #1 in Table 4), significant differences of ADI distributions ($p < 0.0001$) at all these residue levels were observed. The estimated mean ADI with respect to consumption of mean $IMI_{RPF}$ increased from 66 to 91 ng/kg/day (38% increase) in the USCC data set. However, we do not observe the same significant differences using the USDA/PDP residue data in which the mean ADI with respect to consumption of mean $IMI_{RPF}$ increased from 202 to 215 ng/kg/day (7% increase).

To our best knowledge, this is the first study aiming to estimate the daily intake of total neonic from fruit and vegetable consumption based on the U.S. population. We found the estimated average daily intake (ADI) of imidacloprid-equivalent total neonic ($IMI_{RPF}$) using residue data from the USCC study were lower than those using USDA/PDP data set. One of the reasons for such disparity is that fruits and vegetables served in the US Congressional cafeterias were provided by a food service company that advertises sustainable food practices and source organically grown agriculture.[20] Whereas food commodities collected by USDA/PDP are intended to supply general supermarkets and grocery stores across the country and therefore may be more representative of typical U.S. consumption. Regardless, the estimated ADIs of $IMI_{RPF}$ using either USCC, USDA/PDP, or the combined data set were significantly lower than the existing cRfD of imidacloprid.

Intuitively, this outcome would be interpreted as the daily total neonic intake via fruit and vegetable consumption at the U.S. population level unlikely to pose an appreciable risk of adverse health effects over a lifetime. However, we are aware that the uncertainties embedded in the analysis that may alter such conclusion in the event that one of the following circumstances is existed. First of all, if more neonic residue data for fruits and vegetables collected from more diverse sources were available, the distributions of ADI of total neonic intake are likely to shift to the right from those estimated values as shown in Figure 2. This scenario seems plausible given the fact that both USCC and USDA/PDP residue data sets only covered a small portion of fruits and vegetables that were consumed by NHANES participants. Even with the expansion of the sampling years to include NHANES 2013 and 2014 for USDA/PDP analysis, the results presented here were still not sufficient for implication on the total fruit and vegetable consumption. Furthermore, we did not take into account other possible dietary sources, such as the consumption of other crops and drinking water in which a recent article reported ubiquitous presence of three neonics, clothianidin, imidacloprid, and thiamethoxam, in finished water samples at concentrations ranging from 0.24 to 57.3 ng/L.[21]

Second, had more precise and sensitive analytical methods with substantially lower LODs for neonics been used by the USDA/PDP, it is likely that many ND samples as reported by USDA/PDP would have become detectable with concentrations higher than the one-half of the LODs that we assigned for the purpose of model simulation. This would have direct impact on the upward estimation of ADI distributions for total neonic. As we compared the uncertainties originated from the selection of LODs in the sensitivity analysis, we found it is evident that the USCC data set gave more stable ADI estimates regardless of how the ND samples were managed, but this is not the case for the USDA/PDP data set. One plausible explanation is that USCC study utilized the analytical method with LODs that are 2 to 3 orders of magnitude lower than those used by the USDA/PDP for the same neonic (Table 1). That led to 91% of detection for the USCC samples were detectable with at least one of the six neonics whereas only approximately 15% of USDA/PDP samples were above the LODs. Therefore, we have to arbitrarily assign the values of one-half of their respective LOD for simulation. We are also aware that USDA/PDP data sets are aimed for risk monitoring and management, not for risk assessment, and therefore higher LODs close to the regulatory level have been used. However, for the interest of public health, the more comprehensive and precise USDA/PDP data set is essential so it could be used to generalize the dietary risk assessment for the U.S. population.

Lastly, in the future event when cRfD were to be revised lower based on the growing evidence of toxicological effects of neonics in mammals, the results obtained from the model simulation may became highly relevant to public health. This is because the existing cRfDs of neonics were established based on observed end points listed in Table 1, which have very little or no relevance to the known toxicological mechanism of neonics that is functioned as the nAChR agonists.

Even though neonics are known to be less selectively bound to mammalian nAChR, it is possible that the inhibition of nAChR would occur at lower levels of neonic exposure than those observed end points. Under the current cRfDs for neonics, the issue of ND data resulting from the elevated LODs might not be a matter for concern because the estimated ADIs are significantly lower than those cRfDs. However, if results from the future toxicological or epidemiological studies


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prove the hypothesis that the inhibition of nAChR or other neurological adverse outcomes could take place at lower NOAELs as shown in Table 1, the revision of cRfDs for neonics to lower levels would be necessary in order to better reflect biologically plausible end points and subsequently to better protect public health. Under this circumstance, the issue of the sensitivity of analytical methods used to analyze neonics in fruits and vegetables would become critically important. This is because a sensitive analytical method would be essential to quantify neonic residues in foods at levels that are allowed to compute ADI with great confidence in order to compare to the cRfDs.

In this study, we demonstrated a methodology designed to simulate human dietary intakes of total neonic by linking residue data with fruit and vegetable consumption patterns. There are two practical approaches that we used in order to facilitate the estimation of the average dietary intake (ADI) of total neonic. First of all, we adopted the validated NCI method[18] for estimating the distribution of long-term ADI of food items among the population using the NHANES two 24-h dietary recalls. It is generally agreed that when using these short-term recall measurements to estimate UI, 24-h recall intake is an unbiased estimate of the long-term UI,[22] and by repeating the measurements of recalls from an individual, the within-person variations should be canceled out. However, we should also note that NCI method assumed no misclassification of respondent's food intake even though this ideal scenario would most likely to be violated giving the nature of using recall data. Although the 24-h dietary recalls could capture more comprehensive and detailed information about all food consumption by the respondents in the past 24 h, the memory dependent interview leading to potential recall bias (e.g., bad estimation of consumed food portion, bias reporting of food types based on knowledge of nutritional values) and interviewers' bias (whether they were well-trained to conduct the interview) should not be neglected.[23,24]

Second, we applied RPF approach to integrate individual neonics found in the same fruit or vegetable sample into a single metric that is corresponding to the imidacloprid-equivalent total neonic, or $IMI_{RPF}$. This RPF approach has been used for integrating a mixture of chemicals that share the same toxicological mode of action, such as PAHs[8] or dioxins,[9] and has recently been applied in assessing neonics in pollen collected from honeybees based on relative lowest-observed-adverse-effect-level (LOAEL).[16] By integrating all neonics into an imidacloprid-equivalent total neonics, the reported value of $IMI_{RPF}$ in each food item is no longer a simple summation of individual neonic residues, but encoded with the cumulative toxicity of all six neonics via fruits and vegetable consumption.

We calculated RPFs based on the comparison of individual neonic's cRfD with imidacloprid's cRfD. We used relative cRfD rather than the relative no-observed-adverse-effect-level (NOAEL) or LOAEL because cRfD is independent from species used in the toxicological studies and therefore is more suitable for the application in integrating human exposure to total neonic. Since U.S. EPA uses cRfD in their regulatory framework for assessing daily exposure to human population without an appreciable risk of adverse noncancer health effects over a lifetime,[25−27] using cRfD in the RPF calculation adjusted for the uncertainties arising from interspecies, intraspecies, subchronic to chronic experiments, and incomplete to complete database.

We acknowledge that the methodology and the residue and consumption databases that we utilized for estimating the ADIs of total neonic comes with several limitations. First of all, the USDA/PDP residue data set offers more fruit and vegetable samples; however, a large portion of those samples were either ND or with very low frequency of detection of any neonic. As we replaced ND samples with one-half of their respective LODs in the main analyses, it occurred quite often that the average $IMI_{RPF}$ for less frequently detected items remain positive and sometimes even higher levels than more frequently detected items. This problem would have been prevented had more sensitive analytical methods with lower LODs been used for USDA/PDP samples. Per our own research experience, we have developed an analytical method with LODs that are two-3 orders of magnitude lower than those used by the laboratories contracted with USDA/PDP without any technical difficulties or cost issues.[28] In order to improve the robustness of the ADI simulation for total neonics, it is necessary to lower the LODs so the ADI estimates would not be affected by how the ND data is managed.

The second limitation has to do with the use of NHANES consumption information in which two 24-h dietary recalls from the same participants were collected within 3−10 days. Although the collection of dietary recalls in consecutive days could be reflective of random daily consumption, by no mean that it reflects the seasonal or annual consumption patterns both qualitatively and quantitatively. Besides, we did not adjust for other participants' characteristics (such as race, gender, or ages) in the analyses. As we stratified all participants by consumption items, further adjustment for other covariates would lead to nonidentifiability of the covariates' effects in certain food items, especially in the analyses of food items that are less likely to be consumed. However, since we are interested in an inference for the general population, the variabilities within population were still reflected by the body weight, in which were presented in the ADI cumulative distribution.

In conclusion, the results from this study imply that the current dietary intakes of total neonic at the population level do not impose a safety concern under the current cRfD established for imidacloprid. The model simulation coupled with the uses of UI and RPF that we demonstrated in this study is merely the first step toward the development of a robust dietary risk assessment for total neonics. We recommend that future research should focus on: (1) collecting more and better-quality residue data as an intervention to the elevated LOD issue seen with the USDA/PDP data set and (2) better understanding the biologically relevant toxicological thresholds of neonics in mammals in order to reduce the uncertainty in the cRfD establishment. Since neonics have been, and most likely will continue to be, the most widely used insecticides worldwide in the future given its increasing rate of usage,[29,30] it is logical to expect the ubiquity of neonic residues in foods that individuals consume daily. Therefore, the importance of carrying out routine dietary intake assessment for total neonic at the population level should not be ignored.

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**Notes**

The authors declare no competing financial interest.

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## ■ ABBREVIATIONS USED

ADI,average daily intake
BW,body weight
CDC,Centers for Disease Control and Prevention
cRFD,chronic reference dose
EPA,Environmental Protection Agency
$IMI_{RPF}$,relative potency factor with respect to imidacloprid
LOAEL,lowest-observed-adverse-effect-level
LOD,limit of detection
nAChR,nicotinic acetylcholine receptor
NCI,National Cancer Institute
ND,nondetectable
Neonic,neonicotinoid
NHANES,National Health and Nutrition Examination Survey
NOAEL,no-observed-adverse-effect-level
PAH,polycyclic aromatic hydrocarbon
PDP,Pesticide Data Program
RPF,relative potency factor
UI,usual intake
USCC,United States Congress Cafeteria study
USDA,United States Department of Agriculture
WTDRD1,NHANES participant's weight for day 1 dietary data
WTDR2D,NHANES participant's weight for both days 1 and 2 dietary data

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