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Potential human exposures to neonicotinoid insecticides: A review

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ABSTRACT

Due to their systemic character and high efficacy to insect controls, neonicotinoid insecticides (neonics) have been widely used in global agriculture since its introduction in early 1990. Recent studies have indicated that neonics may be ubiquitous, have longer biological half-lives in the environment once applied, and therefore implicitly suggested the increasing probability for human exposure to neonics. Despite of neonics' persistent characters and widespread uses, scientific literature in regard of pathways in which human exposure could occur is relatively meager. In this review, we summarized results from peer-reviewed articles published prior to 2017 that address potential human exposures through ingestion and inhalation, as well as results from human biomonitoring studies. In addition, we proposed the use of relative potency factor approach in order to facilitate the assessment of concurrent exposure to a mixture of neonics with similar chemical structures and toxicological endpoints. We believe that the scientific information that we presented in this review will aid to future assessment of total neonic exposure and subsequently human health risk characterization.

1. Introduction of neonicotiniod insecticides

Neonicotinoid insecticides (neonics) were first introduced in 1990s, and have quickly become one of the most widely used insecticides worldwide in agriculture, veterinary, and residential environment because of their high efficacy for insect controls and the ease of application (Simon-Delso et al., 2015). It was estimated in 2008 that neonics were accounted for more than 20 percent and €6.633 billion of the global insecticide market (Jeschke et al., 2010). Neonics are often applied either by spraying, drip irrigation, or *via* seed treatment. In recent years, the proportion of corn and soybean seeds pre-treated with neonics was up to 90% and 44-50%, respectively in the United States (Chen et al., 2014; Douglas and Tooker, 2015; Hladik et al., 2014; Hurley and Mitchell, 2015; Krupke et al., 2012; Simon-Delso et al., 2015), whereas in the European Union, approximately 20% of neonics was used for seed treatment and drip irrigation (Arnold et al., 2012).

The primary mode of action of neonics is to act on the nicotinic acetylcholine receptors (nAChRs) in the central nervous system, subsequently leading to neurobehavioral deficits and the increased expression of glial fibrillary acidic protein in the motor cortex and hippocampus (Abou-Donia et al., 2008; Li et al., 2011). However, the expression of GFAP in the motor cortex and hippocampus as reported by Abou-Donia et al. (2008) required more rigorous evaluation in order to support the findings. According to U.S. EPA's risk assessments, acetamiprid is neurotoxic and also associated with liver, kidney, thyroid, testicular, and immune system effects in mammals (USEPA, 2007–2012). Thiacloprid has been designated as “Likely to be Carcinogenic to Humans,” with thyroid tumors observed in male rats and uterine tumors in rats and ovarian tumors in mice (USEPA, 2003). Besides those adverse neurodevelopmental, immune, and cancer endpoints, the phenomenon of sub-lethal toxicity of thiamethoxam, clothianidin, and thiacloprid has been observed in honeybees in the form of impaired navigation performance, social communication, and reproductive capacity (Straub et al., 2016; Tison et al., 2016).

Recent studies have indicated that neonics have longer biological half-lives in the environment and therefore might be ubiquitous than previously thought (EU, 2013). This is because once

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applied; neonics could be retained in water or soil over a long period of time without being degraded. The biological half-lives of clothianidin and imidacloprid in soils were a few months and two to three years, respectively, as reported by Hopwood et al. (2012). A recent study conducted by the U. S. Geological Survey (USGS) has shown that at least one neonic was detected in 53% of surface water collected from streams nationwide in which imidacloprid is the most frequently detected neonic (37%), followed by clothianidin (24%), thiamethoxam (21%), dinotefuran (13%), and acetamiprid (3%) (Hladik and Kolpin, 2015). Those residue levels of neonics in local streams as reported by the USGS study were higher than organophosphates and carbamates as reported in the previous investigations of similar land-use areas and associated with crop planting in nearby farmland (Hladik et al., 2014). Therefore, those field data collectively suggested that neonic concentrations in surface water bodies would have increased over the years due to the extended biological half-lives in water and the repeated applications of neonics in agricultural lands. Consequently, it would increase the probability for human exposure to neonics.

Because of their systemic character by design, neonics once applied are absorbed mainly by the roots and then distributed to all tissues of plants (Sánchez-Bayo, 2014), including leaves, root, pollen, flowers, and the fruits/crops of various plants (Schmuck and Lewis, 2016). This is why neonics are popular in the seed treatment application in which a variety of seeds are treated with neonics prior to planting. From the pest control perspective, neonics seem to offer advantages of the ease of application and the efficacy of absorption by the plants over other insecticides. However, from the concern of ecological and human exposures, neonics will no doubt affect non-target organisms that may come in contact with the plant products. Therefore, for the reasons of systemic property and the popularity in insect controls, it is rational to anticipate the ubiquitous of neonics in the environment and in the foods that have been treated with neonics.

Despite of their widespread uses, the information on human exposures to neonics and the potential human health effects are relatively lacking. A PubMed search of related articles of neonics has yielded to a total of 673 publications published before January 2017 in which less than 100 papers of those are relevant to this review (Fig. 1). The purposes of this review are three-folded. First of all, we aim to illustrate the potential pathways for human exposure to neonics. Secondly, we re-introduce a methodology, relative potency factor (RPF), in order to facilitate assessing aggregate exposure and cumulative risks of total neonic. Lastly, we hope that this review will serve as a stimulant for future research engaging in human exposure and risk assessments for neonics.

2. Data source and study selection

We conducted a literature search in PubMed for articles written in English and published prior to 1/1/2017. We used the following keywords to identify relevant articles: [Human exposure, residue, fruit and vegetable, water, soil, tea, pollen, urine or biomonitoring] AND [Neonicotinoid], which leads to a total of 673 papers. We then screened all abstracts to determine their suitability for this review. In order to concentrating on identifying the possible human exposure pathways of neonics, we excluded articles only demonstrating ecological effects resulting from neonics exposure, the development of analytical methods for neonics without any relevance of potential human exposure, or only reporting qualitative data (yes or no detection of neonics). Two authors of this article (Q. Zhang and C.H. Chang) independently retrieved and screened all the titles and abstracts of papers according to the selection criteria. Any discrepancies were resolved by consensus (Fig. 1).

3. Relative potency factor (RPF) approach for assessing total neonic exposure

While almost all papers that we reviewed and included in this article reported individual levels of neonic in various environmental media and foods, it poses a limitation for assessing total neonic exposure under the circumstance when a mixture of different neonics are present concurrently. Although the simple arithmetic summation of individual neonics is a convenient approach to reflect the total neonic exposure, it underestimates the true risk of neonic exposure when more toxic neonics are present in the same sample with other less toxic neonics. Therefore, we recognized a methodology is needed to integrate all neonic residues by taking into account the differences of toxicity for individual neonics.

The US Environmental Protection Agency (USEPA) has developed a relative potency factor (RPF) approach for assessing health risks associated with exposures to a mixture of chemicals with similar molecular structures and the same mode of action (or toxicological endpoints), such as dioxin, polycyclic aromatic hydrocarbons (PAHs), organophosphorous (OPs) or synthetic pyrethroid (SPs) pesticides (Barron et al., 2004; Blaznik et al., 2016; Boobis et al., 2008; EFSA, 2008; EFSA, 2009; Staskal et al., 2010; USEPA, 2008; Wolansky et al., 2006). The principle of RPF is to normalize the potencies of each chemical within a cumulative assessment group to an index compound in which should be a chemical that is well studied with an extensive toxicological database. Since RPF methodology has been used to assess aggregate exposures and cumulative risks of pesticides to human health (Boobis et al., 2008; EFSA, 2008; EFSA, 2009), we think applying RPF approach is a logical outgrowth and highly pertinent to assessing the exposure and risk of total neonic.

In order to demonstrate how the RPF approach could facilitate assessing total neonic exposure and comparing results across studies, we have made attempt to calculate the RPF-adjusted imidacloprid, or IMI_{RPF}, based on data in the published papers using Equation (1) and then reported in this review, as shown in Fig. 2.

$$\begin{aligned}IMI_{RPF}\ (\mu g/kg) = \Sigma_i\ (neonics_i \text{ x } RPF_i) = \text{imidacloprid} + \\ \text{imidaclothiz} + \text{thiamethoxam} \times 9.5 + \text{acetamiprid} \times 0.8 + \\ \text{clothianidin} \times 5.8 + \text{thiacloprid} \times 14.2 + \text{dinotefuran} \times 2.9 \qquad (1)\end{aligned}$$

in which $RPF_i = RfD_{imidacloprid}/RfD_i$.

We chose imidacloprid as the index neonic not only because it is the most commonly used neonic worldwide, but also because it is the most well-studied in regard of its toxicity among the neonics (van Dijk et al., 2013; Lu et al., 2016; Cimino et al., 2016). As shown in Equation (1), the concentrations of IMI_{RPF} will be higher than the values of direct summation when thiacloprid, thiamethoxam, dinotefuran, or clothianidin is also present in the samples. This is because those 4 neonics are considered more toxic (Table S1) with higher relative potency factors based on their reference doses (RfD) as shown in Tables 1–3 than imidacloprid itself. Without calculating IMI_{RPF}, it is also not possible to allow for comparing results across different studies conducted in different countries that bear risk implications.

4. Potential pathways for human exposure to neonics

4.1. Ingestion exposure

One of the advantageous characters of neonics over other agrochemicals is the systemic property in which neonics can be absorbed by the roots of the plants via directly application to the soil or through seed coating. However, the systemic character itself