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Effects of chronic exposure of *Caenorhabditis elegans* to neonicotinoids (imidacloprid, dinotefuran) over multiple generations

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Abstract

Neonicotinoids are potent agonists of nicotine acetylcholine receptors and exert insecticidal effects by causing abnormal excitation of the nervous system. Recently, their effects on mammals, including humans, have become of concern. In the present study, we evaluated the effects of chronic exposure to two neonicotinoids, imidacloprid (IMI) and dinotefuran (DINO), using *Caenorhabditis elegans* as the model organism. We used 1, 10, 100, and 1000 μM solutions of nicotine, IMI, and DINO dissolved in 1% DMSO. Bioassays (growth, maturation, and reproduction tests) were performed on the L1-L2 larvae of wild-type *C. elegans*. To evaluate the effect of exposure over multiple generations and the correlation between concentrations and generations, the same study was conducted in second and third generations of the exposed group. The bioassay results showed concentration-dependent adverse effects at concentrations above 10 μM for both IMI and DINO in both tests for one generation. In the multi-generation study, the effect intensified with the progression of generations, and the toxicity of both IMI and DINO was cumulative. This effect was more pronounced in the breeding study, with significant adverse effects comparable to those of nicotine between generations at concentrations ≥1 μM. This study showed that neonicotinoid concentrations within crop residue limits can adversely affect ecosystem organisms. We suggest that chronic exposure to neonicotinoids may have adverse effects across generations, particularly on reproductive performance. These findings suggest the need to conduct a comprehensive toxicity assessment, including genetic analysis, such as RNA sequencing and real-time PCR, in the future.

Keywords : *Caenorhabditis elegans*, neonicotinoids, imidacloprid, dinotefuran, multigenerational effects

I Introduction

Since their development in the 1990s as substitutes for organophosphorus pesticides, neonicotinoids have been registered as pesticides in approximately 120 countries and are the most widely used pesticides worldwide[1, 2]. Neonicotinoid is the generic name for chloronicotinyl pesticides[3], and were created based on the structure of nicotine. Imidacloprid (IMI), the first neonicotinoid released in the market, is the best-selling insecticide worldwide. IMI is classified as a chloronicotinyl insecticide and has a chloropyridine ring and a nitro group. In Japan, IMI was launched in 1992[4], acetamiprid and nitenpyram in 1995[5, 6], and thiacloprid in 2001[7] as chloronicotinyl insecticides. These were followed by thianicotinyls; thiamethoxam was launched in 2000[8] and clothianidin was launched in 2001[9] as a thianicotinyl compound having a chlorothiazole ring. In 2002, dinotefuran (DINO), a third-generation neonicotinoid with a tetrahydrofuran ring instead of a chloropyridine or chlorothiazole ring, which was previously thought to be an essential structural element for neonicotinoid action, was launched. Seven types of neonicotinoids have been registered[10]. The structures of IMI and DINO are shown in Fig. 1.

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