Neonicotinoid pesticides

- 1991: Imidacloprid
- Neurotoxines
- Systemic action

*Systemic = crop takes it up into its plant sap: chemical makes plant toxic from inside*
Toxicity of insecticides to honeybees compared to DDT. The final column expresses the toxicity relative to DDT. (Source: Bonmatin, 2011)

| pesticide          | ®         | Use       | Dose g/ha | LD50 ng/ab | Tox/DDT |
|--------------------|-----------|-----------|-----------|------------|---------|
| DDT                | Dinocide  | insecticide | 200-600   | 27 000.0   | 1       |
| thiaceclopride     | Proteus   | insecticide | 62.5      | 12 600.0   | 2.1     |
| amitraze           | Apivar    | acaricide  | -         | 12 000.0   | 2.3     |
| acetamiprid        | Supreme   | insecticide | 30-150    | 7 100.0    | 3.8     |
| coumaphos          | Perizin   | acaricide  | -         | 3 000.0    | 9       |
| methiocarb         | Mesurol   | insecticide | 150-2200  | 230.0      | 117     |
| tau-fluvalinate    | Apistan   | acaricide  | -         | 200.0      | 135     |
| carbofuran         | Curater   | insecticide | 600       | 160.0      | 169     |
| λ-cyhalothrine     | Karate    | insecticide | 150       | 38.0       | 711     |
| thiaméthoxam       | Cruiser   | insecticide | 69        | 5.0        | 5 400   |
| fipronil           | Regent    | insecticide | 50        | 4.2        | 6 475   |
| imidaclopride      | Gaucho    | insecticide | 75        | 3.7        | 7 297   |
| clothianidine      | Poncho    | insecticide | 50        | 2.5        | 10 800  |
| deltamethrine      | Décis     | insecticide | 7.5       | 2.5        | 10 800  |

Toxicity of insecticides to honeybees compared to DDT. The final column expresses the toxicity relative to DDT. (Source: Bonmatin, 2011)
Imidacloprid 2010 World production: 20,000 tonnes (DDT peak-use 80,000 tonnes in 1959)

Figure 4
Changes in use of insecticide classes between 1997 and 2010 showing decreases for organophosphates (OPs), methylcarbamates (MCs), and pyrethroids (pyr) and increases for neonicotinoids (neonic) and other compounds. Abbreviations: AChE, acetylcholinesterase; nAChR, nicotinic acetylcholine receptor. Data shown for the years 1997, 2000, 2002, 2005, 2008, and 2010 from T.C. Sparks (personal communication) are similar to those from his coauthored paper (95).
## Market shares

| Product      | Crop uses | Company                  | 2003 | 2005 | 2007 | 2009 |
|--------------|-----------|--------------------------|------|------|------|------|
| imidaclorpid | 140       | Bayer CropScience        | 665  | 830  | 840  | 1091 |
| thiamethoxam | 115       | Syngenta                 | 215  | 359  | 455  | 627  |
| clothianidin | 40        | Sumitake / Bayer CS      | <30  | 162  | 365  | 439  |
| acetamiprid  | 60        | Nippon Soda              | 60   | 95   | 130  | 276  |
| thiacloprid  | 50        | Bayer CropScience        | <30  | 55   | 80   | 112  |
| dinotefuran  | 35        | Mitsui Chemicals         | <30  | 40   | 60   | 79   |
| nitenpyram   | 12        | Sumitake                 | 45   | <10  | <10  | 8    |

**Figure 1.** Changes in the market share (billion Euros) of the major insecticidal classes used in crop protection between 1990 and 2008. Adapted from Jeschke *et al.* 2011.
Growth in the agricultural use of neonicotinoid insecticides in Britain from 1990, measured in tonnes of active ingredient applied per year. Data from http://pusstats.csl.gov.uk/index.cfm
Imidacloprid use on farms. Darker color indicates greater quantity used per square mile.

Source: USGS National Water-Quality Assessment Program Pesticide National Synthesis Project, http://water.usgs.gov/nawqa/pnsp/usage/maps/compound_listing.php (accessed 9/16/13).
Only 1.6 to 20% of applied neonicotinoid is absorbed by the growing crop (Sur & Stork 2003) 80 to 98.4% leaches to soil & water!

Since 2004, Netherlands surface water is heavily polluted with Imidacloprid

www.bestrijdingsmiddelenatlas.nl

![Maps showing Imidacloprid in Dutch surface water 2003-2008](images) Exceedances of the Maximum Tolerable Risk standard MTR = 13 nanogram / liter
Exposure non-target organisms

Exposure Paths
Exposure of non-target organisms to systemic pesticides can occur via multiple pathways, of which some are shown below:

- Particles in the air during sowing
- Treated plant
- Contamination of the soil
- Contamination of surface and groundwater
- Treated seeds
- Nectar
- Pollen
- Guttation or Honeydew
Findings on aquatic ecosystems

• Permanent leaching of Imidacloprid year round from fields to surface water
• 45% of all samples ($n=9037$) on all ($n=801$) Dutch measurement locations had imidacloprid concentrations that exceed the MTR (>13 ng/liter)
• 70% reduction in macrofauna abundance in polluted water
• Meeting MTR requires reduction of use by at least 90%.

Van Dijck et al., 2013
Findings on pollinators

• Global pollinator decline multifactorial
• At field realistic concentrations, neonicotinoids produce wide range of adverse sublethal effects in bees, affecting colony performance through impairment of foraging success, brood, larval development, memory and learning, susceptibility to diseases, hive hygiene, etc.
• Clothianidin weakens the immune response in bees and promotes replication of a viral pathogen in bees.
• 85% reduction in bumblebee queen production could be a key factor explaining global trends of bumblebee decline.
• Few studies assessed toxicity to other wild pollinators. Available data suggest that they are likely to exhibit similar toxicity to all wild insect pollinators.
• Pollination is of vital importance both for natural ecosystems and farming.

Di Prisco et al., 2013; Lautenbach et al., 2012; Whitehorn et al., 2012; Adamski et al., 2009
Findings vertebrates

- Direct (toxicity) / indirect (reduced food supply)
- mammals, birds, fish, amphibians, reptiles
- wide range of sub-lethal effects: from reduced growth and breeding success, to immunotoxic and genotoxic effects at concentrations $< \text{LD50}$
- In general: exposure $< \text{LC50}$
- Exposure $> \text{LD50}$ possible for granivorous birds
- Multiple routes of exposure
- Population level effects under explored
- One study demonstrated population level effects of fipronil on lizard populations via invertebrate decline (Peveling et al. 2003)
- Indirect effects may be as - or even more - important than direct toxic effects on vertebrates
Conclusions

• Scale, toxicity and method of use unprecedented
• Persistence in the environment leads to significant exposure levels for non-target organisms
• Proven impacts on pollinators and aquatic invertebrates. Likely to have impacts on biodiversity

ACTION:
Worldwide Integrated Assessment
By Task Force
Grazie mille!
Neonicotinoid clothianidin adversely affects insect immunity and promotes replication of a viral pathogen in honey bees

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Large-scale losses of honey bee colonies represent a poorly understood problem of global importance. Both biotic and abiotic factors are involved in this phenomenon that is often associated with high loads of parasites and pathogens. A stronger impact of pathogens in honey bees exposed to neonicotinoid insecticides has been reported, but the causal link between insecticide exposure and the possible immune alteration of honey bees remains elusive. Here, we demonstrate that the neonicotinoid insecticide clothianidin negatively modulates NF-κB immune signaling in insects and adversely affects honey bee antiviral defenses controlled by this transcription factor. We have identified in insects a negative modulator of NF-κB activation, which is a leucine-rich repeat protein. Exposure to clothianidin, by enhancing the transcription of the gene encoding this inhibitor, reduces immune defenses and promotes the replication of the deformed wing virus in honey bees bearing covert infections. This honey bee immunosuppression is similarly induced by a different neonicotinoid, imidacloprid, but not by the organophosphate chlorpyrifos, which does not affect NF-κB signaling. The occurrence at sublethal doses of this insecticide-induced viral proliferation suggests that the studied neonicotinoids might have a negative effect at the field level. Our experiments uncover a further level of regulation of the immune response in insects and set the stage for studies on neural modulation of immunity in animals. Furthermore, this study has implications for the conservation of bees, as it will contribute to the definition of more appropriate guidelines for testing chronic or sublethal effects of pesticides used in agriculture.

Apis mellifera | DWV | NLR (CLR) | neuroimmunity | toxicity

attention. In particular, neonicotinoid insecticides are currently the subject of intense debate (13). Over the last few years, several countries have restricted their use in agriculture, and they are currently under the close scrutiny of the European Food Safety Authority (14–16); recently, three of them have been temporarily banned by the European Commission (17), based on the growing scientific evidence regarding the negative effects they have on bees. It has been shown that sublethal doses of thiamethoxam can affect the homing capacity of honey bees with negative consequences on colony stability (18). Concurrent studies on bumblebees have provided further confirmation of the hypothesis that neonicotinoids can have a wider negative impact on pollinators (19, 20). Importantly, exposure to neonicotinoids is often associated with a higher pathogenic impact on bees (21–23), although the merely descriptive results reported are somewhat contrasting and do not support any clear epidemiological interpretation, due to significant gaps in our knowledge of if and how these insecticides act on honey bee immunity (24). Here we address this issue, focusing on the mechanism underlying the presumed immunosuppressive activity of neonicotinoids on insects.

Ecotoxicological studies have reported that exposure of Mytilus galloprovincialis to sublethal doses of the neonicotinoid insecticide thiacloprid up-regulates the expression of transcription factors that show sequence similarity with members of the CATHERPILLER (CLR) protein family in mammals (25), subsequently renamed, along with other aliases, as “Nucleotide-binding domain and Leucine-rich Repeat” (NLR) (26). These proteins play an