What Is Known About the Human Health Effects of Neonicotinoid Pesticides?

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Milken Institute School of Public Health
The George Washington University
What are neonics?

- Entirely new type of insecticide: systemic
- Developed mid-90s to replace organophosphates/carbamates
- High potency at low concentrations
- Chemically similar to nicotine
- Bind to nicotinic acetylcholine receptor (nAChR)
- Acetimiprid (ACE), Imidacloprid (IMI), thiamethoxam (THO), clothianidin (CLO)
- Persist in crops and soil

Sources of Exposure
Trend in Neonicotinoid Sales and Use through 2012

Japan Domestic Shipment
California Total Use
Sweden Sales
Britain Agricultural Use

Simon Delso et al., 2015
How are neonics used?

Use of IMI has grown exponentially since its approval in 1994
US Agricultural Use

Imidicloprid
Use by Year and Crop

Clothianidin
Use by Year and Crop

Data retrieved from: Pesticide National Synthesis Project of National Water-Quality Assessment Program (USGS)
Environmental fate of neonic seed dressings

(Source: Goulson)

- 0.5-2% lost as dust (in the environment)
- ~2% absorbed by crop
- ~96% stays in soil or soil water
- Waterways: ~unknown%
Neonics in the environment

Neonics can be highly persistent and transport via soil, water, dust, air, pollen, leaching, & accumulation in non-target species

**Half-life soil:**
- THX: 25-100 days
- IMI: 40-997 days
- CLO: 148-1,155 days

**Half-life water:**
- THX: 8.5 days
- IMI: 30 days
- CLO: 40.3 days
79 Water Samples taken from 9 Iowa Streams over 2013 Growing Season
# Consumer Use

## Examples of Neonicotinoid Garden Products Used in the United States

<table>
<thead>
<tr>
<th>Neonicotinoid</th>
<th>Garden and ornamental uses</th>
<th>Garden Product Trademark names</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imidacloprid</td>
<td>Seed dressing, soil drench, granules, injection, or spray to a wide range of ornamental plants, trees, and turf.</td>
<td>Bayer Advanced 3-in-1 Insect, Disease, &amp; Mite Control&lt;br&gt;Bayer Advanced 12 Month Tree &amp; Shrub Insect Control</td>
</tr>
<tr>
<td>Clothianidin</td>
<td>Seed treatment, foliar spray or soil drench for turf, a variety of ornamental trees, and flowers.</td>
<td>Bayer Advanced All-in-One Rose &amp; Flower Care granules&lt;br&gt;Green Light Grub Control with Arena</td>
</tr>
<tr>
<td>Acetamiprid</td>
<td>Foliar spray for fruits, vegetables, ornamental plants, and flowers.</td>
<td>Ortho Flower, Fruit and Vegetable Insect Killer&lt;br&gt;Ortho Rose and Flower Insect Killer</td>
</tr>
</tbody>
</table>

## Example of Neonicotinoid Animal Care Products Used in the United States

<table>
<thead>
<tr>
<th>Neonicotinoid</th>
<th>Animal Care Use</th>
<th>Trademark Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imidacloprid</td>
<td>Broad spectrum protection against fleas, heartworms, parasites</td>
<td>Advantage</td>
</tr>
</tbody>
</table>
Pets and In-Home Use

- Residue detected in dog’s blood for up to 72 h after application
- Transferrable residue detected on coat for up to 4 weeks

Reference: Craig 2005
Neonics in food

Table 5. Summary of Neonicotinoids Concentrations in Foods

<table>
<thead>
<tr>
<th>analyte</th>
<th>food type</th>
<th>total samples collected</th>
<th>no. of samples &gt; LOQ</th>
<th>freq of detection (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>imidacloprid</td>
<td>fruits</td>
<td>17</td>
<td>15</td>
<td>82</td>
</tr>
<tr>
<td></td>
<td>vegetables</td>
<td>12</td>
<td>7</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td>honey</td>
<td>10</td>
<td>9</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>pollen</td>
<td>13</td>
<td>10</td>
<td>77</td>
</tr>
<tr>
<td>clothianidin</td>
<td>fruits</td>
<td>17</td>
<td>3</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>vegetables</td>
<td>12</td>
<td>3</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>honey</td>
<td>10</td>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>pollen</td>
<td>13</td>
<td>6</td>
<td>46</td>
</tr>
<tr>
<td>thiamethoxam</td>
<td>fruits</td>
<td>17</td>
<td>3</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>vegetables</td>
<td>12</td>
<td>4</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>honey</td>
<td>10</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>acetamiprid</td>
<td>fruits</td>
<td>17</td>
<td>4</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>honey</td>
<td>10</td>
<td>1</td>
<td>10</td>
</tr>
</tbody>
</table>

• Common foods contain multiple neonics, some at levels >MRLs

Chen et al. 2014
Review of Literature

Are Neonicotinoids Reproductive Toxicants?
Temporal Levels of Urinary Neonicotinoid Concentrations in Japanese Women

Reference: Ueyama 2015
<table>
<thead>
<tr>
<th>Objective</th>
<th>Neonicitinoid</th>
<th>Animal</th>
<th>Findings</th>
</tr>
</thead>
</table>
| Najafi (2010) Evaluate chronic effect of IM exposure on testicular tissue, sperm morphology, and testosterone in serum | Imidacloprid | Male rats | Testicles decreased in size and weight*  
Severe hypertrophy and cytoplasmic granulation in Leydig cells  
Difference in Repopulation Index*  
Decrease in normal sperm content, viability of content, and motile sperm content*  
Reduced testosterone * |
| Kapoor (2011) Evaluate effect of IM exposure on ovarian morphology, hormones, and antioxidant enzymes | Imidacloprid | Female rats | Decrease in ovary weight at IMI 20  
Serum FSH was increased*; LH and progesterone decreased in IMI 20  
LPO and decrease in GSH content, SOD, CAT and GPX activity in IMI 20 |
| Bal (2012a) Investigate effect of low doses of CTD exposure on reproductive system | Clothianidin | Male rats (developing) | Epididymal sperm concentration decreased in CTD 32 group*  
Abnormal sperm rates increased in CTD 8 and 32  
Testosterone level decreased in CTD 32*  
Decrease in GSH in all groups*  
TUNEL positive cells increased in CTD 32 |
| Bal (2012b) Investigate effect of low doses of IM exposure on reproductive system | Imidacloprid | Male rats | Deterioration in sperm motility in IMI 8*  
Decrease in epididymal sperm concentration in IMI 2 and 8*  
Increase in sperm morphology in IMI 8*  
Decrease in testosterone and GSH in 8*  
Apoptotic index increase only in germ cells of seminiferous tubules of IMI 8*  
Fragmentation in DNA of IMI8  
Elevation in fatty acids (stearic, oleic, linoleic and arachidonic acids)* |
| Bal (2012c) Investigate effect of IM exposure on DNA fragmentation, antioxidant imbalance, and apoptosis | Imidacloprid | Male rats (developing) | Weight of epididymis, vesicular seminalis, epididymal sperm concentration, body weight gain, testosterone and reduced glutathione values lower in IMI groups;  
Increased peroxidation, fatty acid concentrations and  
Higher rates of abnormal sperm in IMI 8*  
Apoptosis and fragmentation of seminal DNA higher in IMI 2 and 8 |
| Gu (2013) Compare in vitro effects of IM and ACE on reproduction | Imidacloprid, Acetamidprid | Male and female mice | Decrease in motility of spermatozoa  
Minor increase in avg. percentage of DNA fragmented spermatozoa  
Among exposed sperm, 2 Cell embryo, morula, blastocyst formation decreased *  
With consecutive exposure from fertilization to blastocyst formation, decrease in morulae and blastocysts for IMI and ACE |
Human Acute exposure findings

<table>
<thead>
<tr>
<th>First author (year)</th>
<th>Study population</th>
<th>Country of study</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elfman (2009)</td>
<td>19 conifer seedling planters: 17 men, 2 women</td>
<td>Sweden</td>
<td>No clear acute adverse effects reported after 1 week of exposure to IMI-treated seedlings</td>
</tr>
<tr>
<td>Forrester (2014)</td>
<td>1142 exposure cases reported to a TX poison control network from 2000-2012</td>
<td>USA</td>
<td>Of the 1142, 77% were identified as IMI alone or in combination with other neonic. 32 neonic exposures (2.9%) resulted in “serious medical outcomes” including ocular irritation/pain, dermal irritation/pain, nausea, vomiting, oral irritation, red eye, erythema, rash, numbness, and dizziness. Chest pain (2 exposures; 0.2%), hypertension (0.2%), and tachycardia (0.2%) were the most frequently reported serious cardiovascular effects. No deaths reported.</td>
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<td>Mohamed (2009)</td>
<td>68 hospital patients: 61 ingestion, 7 dermal exposures</td>
<td>Sri Lanka</td>
<td>Of the 56 patients with acute IMI poisoning (versus mixtures), only 2 developed severe symptoms. The majority had mild symptoms including nausea, vomiting, headache, dizziness, abdominal pain, and diarrhea. IMI exposure confirmed in 28 cases, with a median plasma concentration of 10.58 ng/L (IQR: 3.84-15.58 ng/L; range: 0.02-51.25 ng/L) on admission. Concentrations for 7 patients remained elevated for 10-15 hours post-ingestion, suggesting absorption and/or elimination may be saturable or prolonged at high doses. No deaths reported.</td>
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<td>Phua (2009)</td>
<td>70 exposure cases reported to the Taiwan National Poison Center</td>
<td>China</td>
<td>Of the 57 cases of ingested neonic, the majority were of IMI (n=53), followed by ACE (n=2) and CLO (n=2). The 10 most severe cases were from IMI alone. Two deaths reported (mortality rate 2.9%).</td>
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AOR: adjusted odds ratio; CI: 95% confidence interval; CrI: credible interval; IMI: imidiacloprid; ACE: acetamiprid; CLO: clothianidin

- Total neonic poisoning exposures n=1280 (698 ingestions, 582 other pathways)
- Mortality n=2
- IMI most common neonic used in self-poisonings (ACE n=8, THO n=6, CLO n=5)
- Traditional pesticide treatments may worsen outcomes for neonic poisonings
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<td>Carmichael (2014)</td>
<td>101 heart defect cases recruited from mothers who participated in a population-based case control study in San Joaquin valley; 9 exposed/92 not exposed</td>
<td>USA</td>
<td>Significant association between residential proximity to agricultural use of IMI and tetralogy of Fallot (AOR 2.4, 95% CI: 1.1-5.4)</td>
</tr>
<tr>
<td>Keil (2014)</td>
<td>407 children with autism spectrum disorder (ASD) recruited from Childhood Autism Risk from Genetics and Environment (CHARGE) Study/ 206 controls</td>
<td>USA</td>
<td>Weak association between prenatal exposure to IMI and ASD (AOR 1.3, 95% CrI: 0.78, 2.2); OR increased to 2.0 (95% CrI: 1.0, 3.9) when limiting study population to those who self-identified as “frequent users” of flea and tick medicines containing IMI</td>
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<td>Marfo (2015)</td>
<td>35 symptomatic cases in Gunma prefecture/ 50 controls</td>
<td>Japan</td>
<td>Significant association between urinary AMP and increased prevalence of memory loss, finger tremor, and other symptoms of unknown origin (OR 14, 95% CI: 3.5-57)</td>
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<td>Yang (2014)</td>
<td>73 anencephaly cases in San Joaquin valley; 6 exposed/67 not exposed</td>
<td>USA</td>
<td>Suggestive association between residential proximity to agricultural use of IMI and anencephaly (AOR 2.9, 95% CI: 1.0-8.2)</td>
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How much neonic is translocated from coated seeds to food, including processed products?

What is the effect of consuming multiple neonics along with other pesticides, some of which are known to increase neonic toxicity?

Are we consuming a hazardous level of neonics & metabolites on a cumulative basis, even at levels <MRLs?

Are certain populations at higher risk due to multiple exposure pathways (e.g., air, water, dust + food) or vulnerable windows of development?

When neonics cross the human placenta are they eliminated or do they bind with nAChR receptors in the fetal brain?
Take Away Points

• Emerging evidence base for ecological impacts and damage to beneficial insects

• Suggestion of reproductive toxicity in vertebrates; sparse mammalian data

• Extremely limited epidemiologic studies

• No human biomonitoring data
Worldwide Assessment of Impact of Systemic Pesticides on Biodiversity and Ecosystems (WIA) 2015

A synthesis of 1,121 published peer-reviewed studies spanning last five years

Including industry-sponsored studies

The single most comprehensive study of neonics

Peer reviewed

Published as open access
From GMO to HFCS to CCD
Dead Bees at the Entrance to a Healthy Hive

Colony collapse disorder hive—with capped honey, an absence of worker bees, but no dead bees
Neonicotinoid sales by product type

Primarily crop chemicals

Neonicotinoid use by crop

Primarily corn and soybeans

Neonicotinoid use by active ingredient

Primarily Imidacloprid, Clothianidin, Thiamethoxam

Reference: Douglas 2015
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Chemical Properties of Neonicotinoids

• Highly water soluble
• Highly volatile in air
• Half-lives > 1,000 days in soil
• Persistence in woody plants for > 1 year
• Pass the placenta and the blood brain barrier

Reference: Bonmatin 2013
# Neonicotinoid Tox21/ToxCast Results ER related assays

<table>
<thead>
<tr>
<th>Cluster</th>
<th>Chemical Name</th>
<th>ER Agonist Area Under Curve (AUC)</th>
<th>ER Antagonist AUC</th>
<th>ER Bioactivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent</td>
<td>Imidacloprid</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Parent</td>
<td>Thiamethoxam</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Parent</td>
<td>Clothianidin</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Parent</td>
<td>Acetamiprid</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Parent</td>
<td>Thiacloprid</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Parent</td>
<td>Dinotefuran</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Parent</td>
<td>(E)-Nitenpyram</td>
<td>not tested</td>
<td>not tested</td>
<td>not tested</td>
</tr>
<tr>
<td>Metabolite</td>
<td>2-Pyridone</td>
<td>not tested</td>
<td>not tested</td>
<td>not tested</td>
</tr>
<tr>
<td>Base</td>
<td>Nicotine</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Base</td>
<td>Nicotine sulfate</td>
<td>not tested</td>
<td>not tested</td>
<td>not tested</td>
</tr>
<tr>
<td>Base</td>
<td>D-Nicotine</td>
<td>not tested</td>
<td>not tested</td>
<td>not tested</td>
</tr>
</tbody>
</table>

*Judson et al., Toxicol. Sci. 148:137–154;*
# Green Screen Evidence Review 2014

<table>
<thead>
<tr>
<th>Target</th>
<th>Reproductive Toxicity</th>
<th>Endocrine Disruption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imidicloprid</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>Clothianidin</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>Thiamethoxam</td>
<td>Moderate</td>
<td>Data Gap</td>
</tr>
</tbody>
</table>
Results: 8 Papers on Reproductive Toxicity/Endocrine Disruption

• Animals
  • Rats (Najafi 2010) (Bal 2012a, b, c) (Rasgele 2014) (Kapoor 2011)
  • Mice (Hirano 2015) (Tanaka 2012) (Gu 2013)

• Neonicotinoid
  • Imidacloripid: (Najafi 2010) (Bal 2012b, c) (Kapoor 2011)
  • Clothianidin (Bal 2012a) (Hirano 2015) (Tanaka 2012)
  • Acetamiprid (Rasgele 2014)
  • Mixture: (Gu 2013)
Seeds, not pounds

- 4 million **pounds** of neonics are applied to between 140 and 200 million acres of cropland annually in US

BUT

- “From 2000-2012, virtually all neonics applied to corn, soybeans and wheat were applied as **seed** treatments” (in US)
  - Neonic seed treatments accounted for approx.
    - 43% of insecticide mass applied to maize by 2010;
    - 21-23% of insecticide mass applied to soybeans by 2011/2;
    - 25-29% of insecticide mass applied to wheat by 2011/2

AND

- Approx. 60% of all neonic application is via seed treatments

Reference: Douglas 2015; Jeschke 2011
Neonics in mammals

- Neonics & byproducts can cross the mammalian blood-brain barrier
- Some neonic metabolites more toxic than parent compound
- Adverse even at sublethal doses, affinity for $\alpha_4\beta_2$ subtype of nAChRs
- Reproductive, genotoxic, cytotoxic, neurobehavioral effects

<table>
<thead>
<tr>
<th>Parent compound</th>
<th>Metabolites</th>
<th>Formation medium</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiamethoxam (TMX)</td>
<td>Clothianidin, CLO</td>
<td>Soil, mice, mammals, insects, plants</td>
<td>Ford and Casida 2006a; Nauen et al. 2003; PPDB 2013; FAO thiamethoxam</td>
</tr>
<tr>
<td></td>
<td>Thiamethoxam-dm, TMX-dm, N-desmethyl thiamethoxam</td>
<td>Mice</td>
<td>Ford and Casida 2006a</td>
</tr>
<tr>
<td></td>
<td>TMX-NNO</td>
<td>Mice, soil bacteria ($Pseudomonas$ sp.)</td>
<td>Ford and Casida 2006a; Pandey et al. 2009</td>
</tr>
<tr>
<td></td>
<td>TMX-NNH2</td>
<td>Mice</td>
<td>Ford and Casida 2006a</td>
</tr>
<tr>
<td></td>
<td>TMX-NH</td>
<td>Mice, soil bacteria ($Pseudomonas$ sp.), water</td>
<td>Ford and Casida 2006a; Pandey et al. 2009; De Uderzo et al. 2007; FAO thiamethoxam</td>
</tr>
</tbody>
</table>

Simon-Delso et al. 2015
Routes of Exposure
Source to Effect Framework

- Sources of stressors
  - Environmental Intensity
  - Time Activity and Behavior
  - Dose

- Upstream Human and Natural Factors

- Effect or Outcomes

Stressors → Exposure → Receptors → Effect or Outcomes