What Is Known About the Exposure and Endocrine Disrupting Properties of Neonicotinoid Pesticides?

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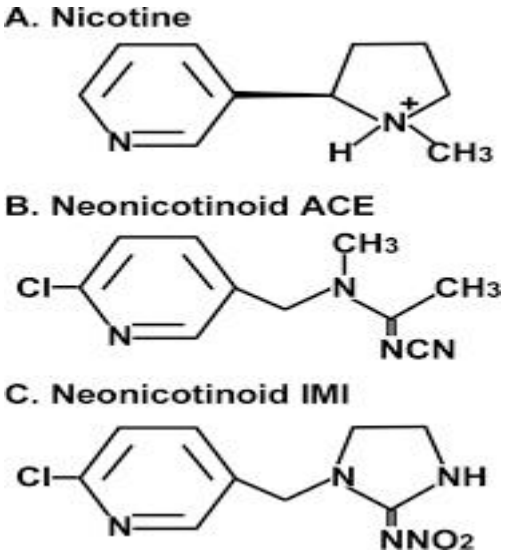
What are neonics?

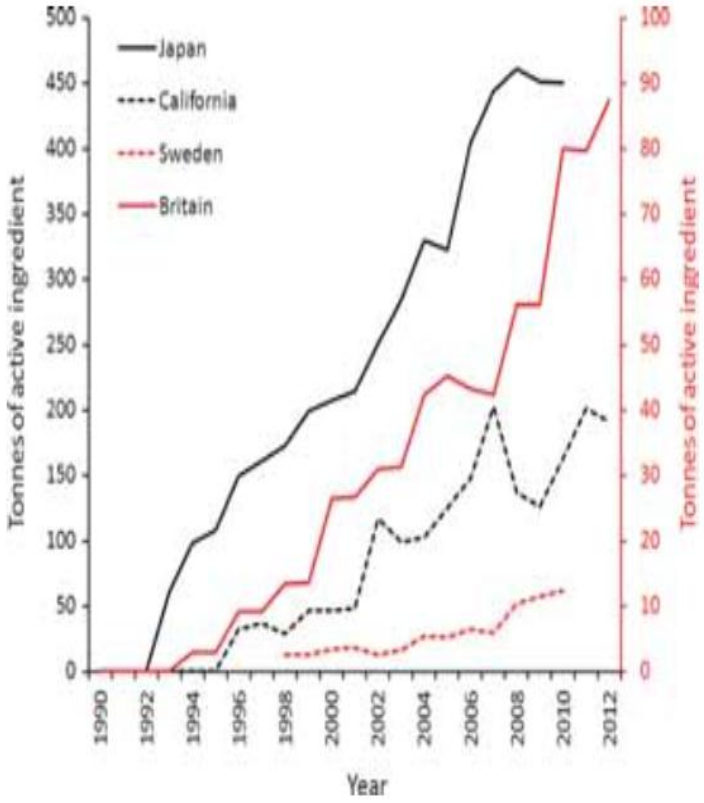
- Entirely new type of insecticide: *systemic*
- Developed mid-90s to replace organophosphates/carbamates
- High potency at low concentrations
- Chemically similar to nicotine
- Bind to nicotinic acetylcholine receptor (nAChR)
- Acetimiprid (ACE), Imidacloprid (IMI), thiamethoxam (THO), clothianidin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



Kimura-Kuroda et al. 2012

Sources of Exposure

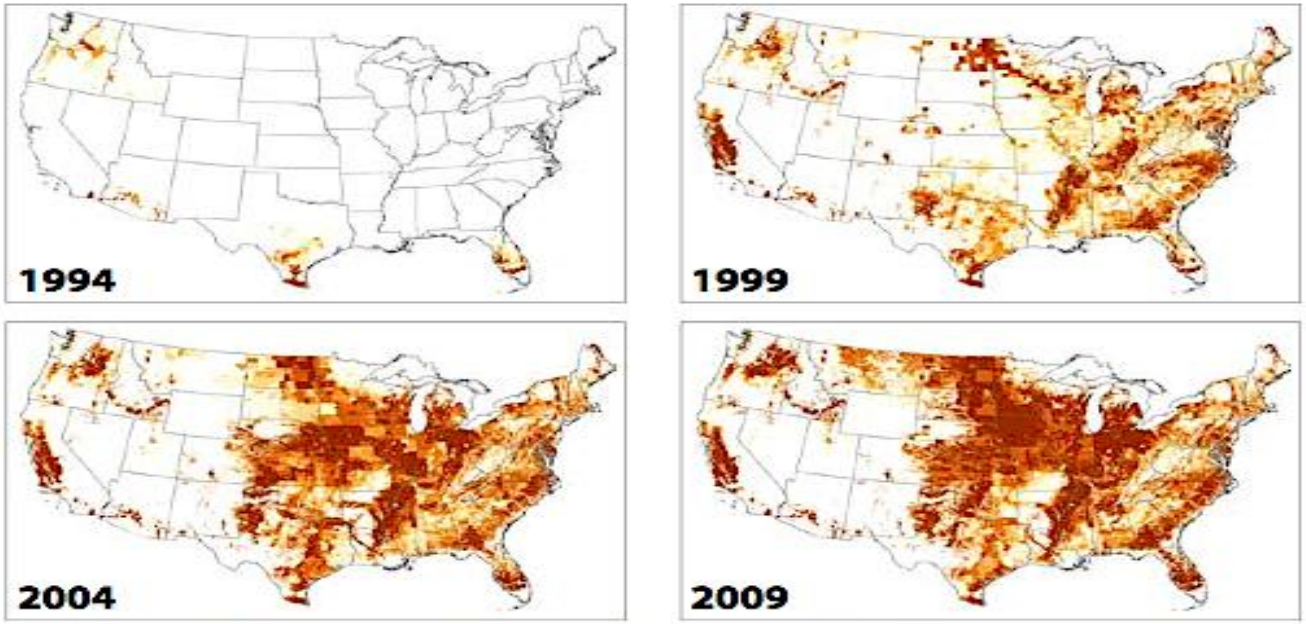
Trend in Neonicotinoid Sales and Use through 2012



Japan Domestic Shipment
California Total Use
Sweden Sales
Britain Agricultural Use

Simon Delso et al., 2015

How are neonics used?

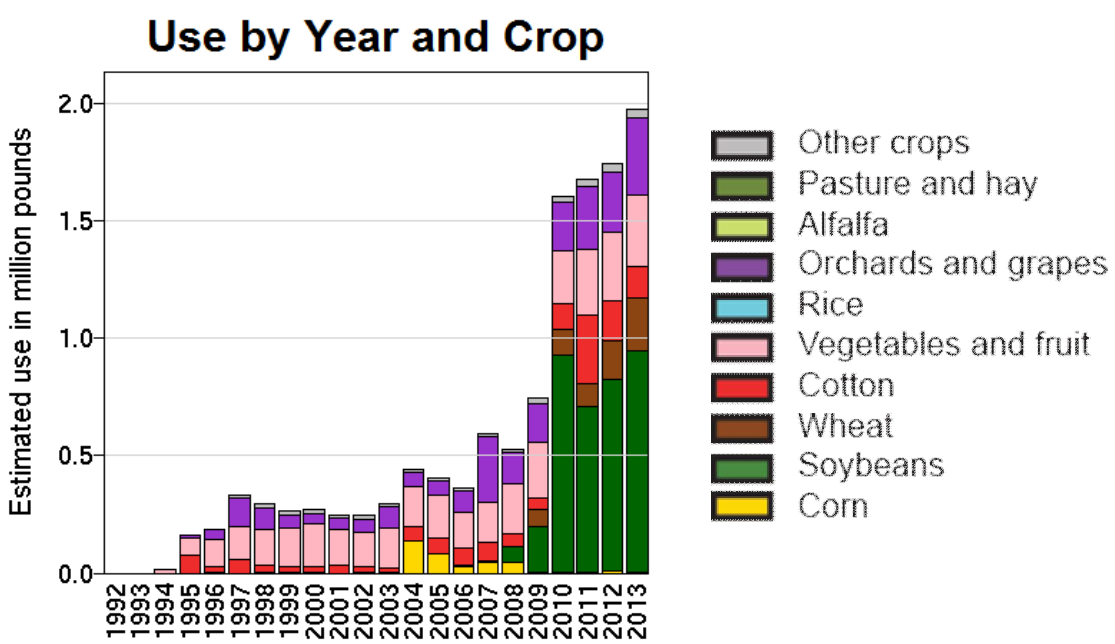


Source: USGS National Water-Quality Assessment Program Pesticide National Synthesis Project, http://water.usgs.gov/nawqa/pnsp/usage/maps/compound_listing.php (accessed 9/16/13).

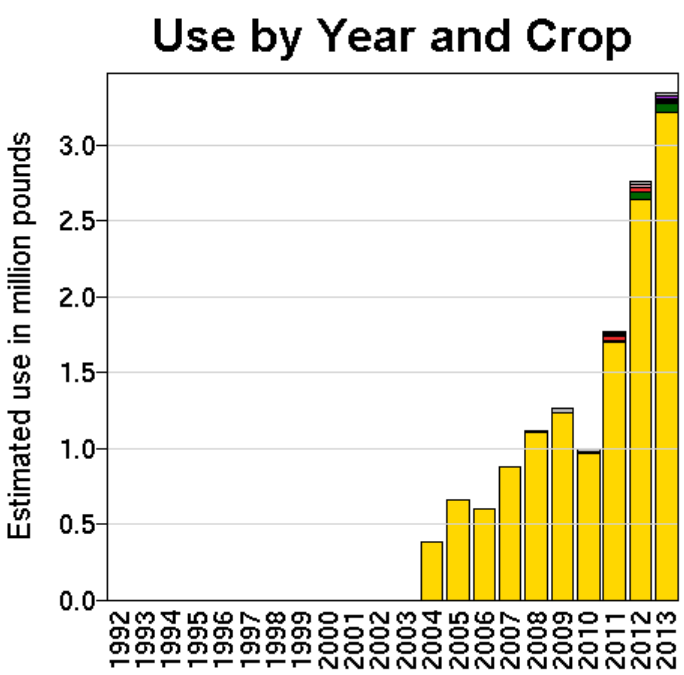
Use of IMI has grown exponentially since its approval in 1994

US Agricultural Use

Imidicloprid



Clothianidin



Data retrieved from: [Pesticide National Synthesis Project of National Water-Quality Assessment Program (USGS)]

Routes of Exposure

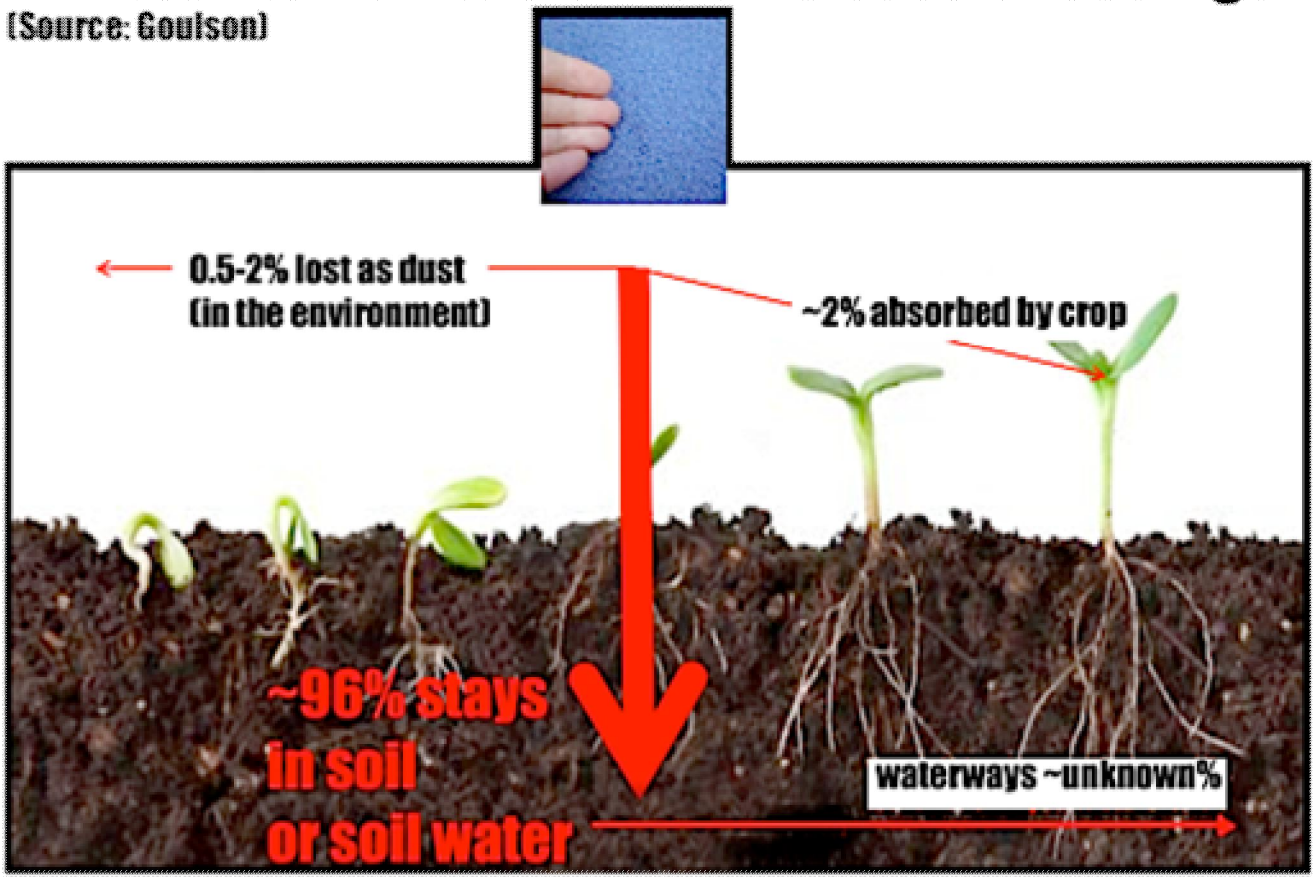
Chemical Properties of Neonicotinoids

- 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

Environmental fate of neonic seed dressings

(Source: Goulson)



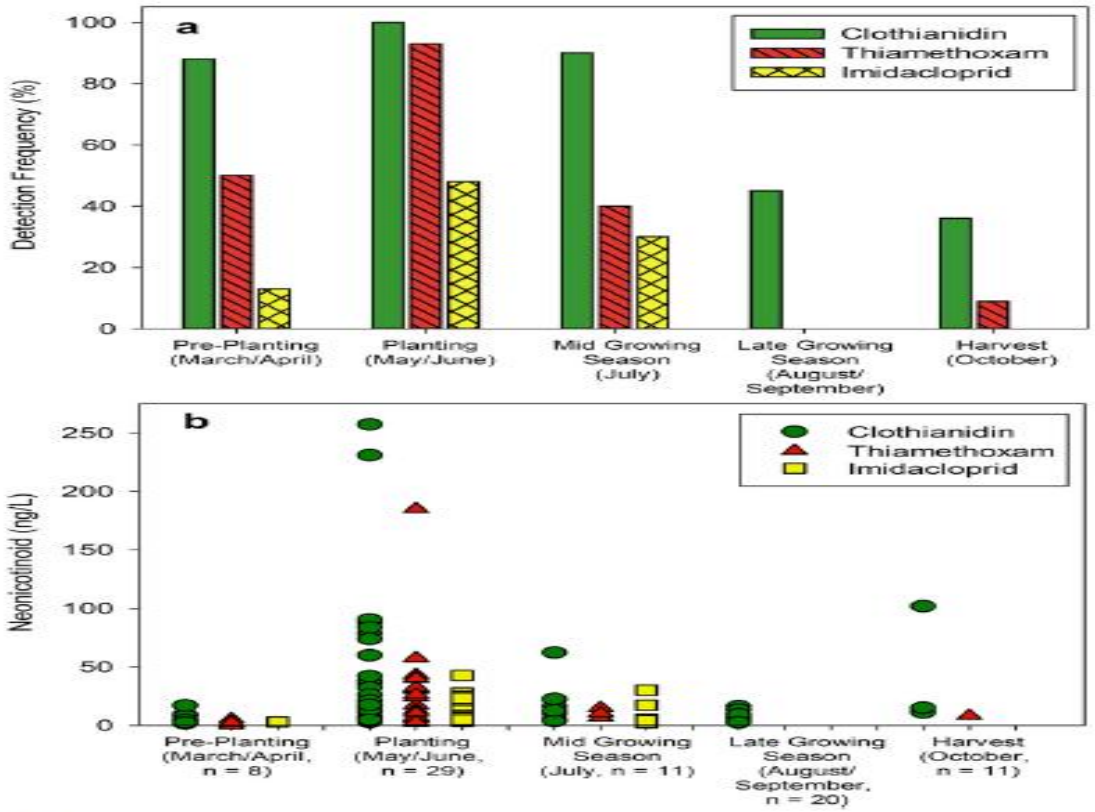
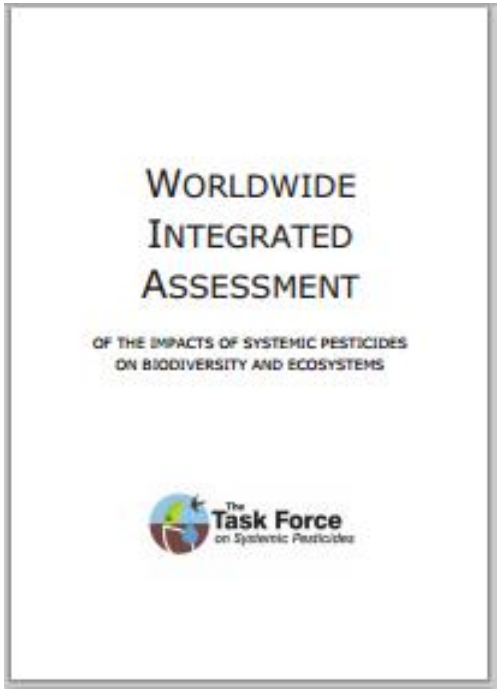


Fig. 5. Summary of (a) detection frequencies and (b) detected concentrations of the three most common neonicotinoids in 79 water samples collected from nine Iowa streams over the 2013 growing season. The number of samples (*n*) during each time period is listed with the detected concentrations (b).

79 Water Samples taken from 9 Iowa Streams over 2013 Growing Season

Hladick et al. 2014

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

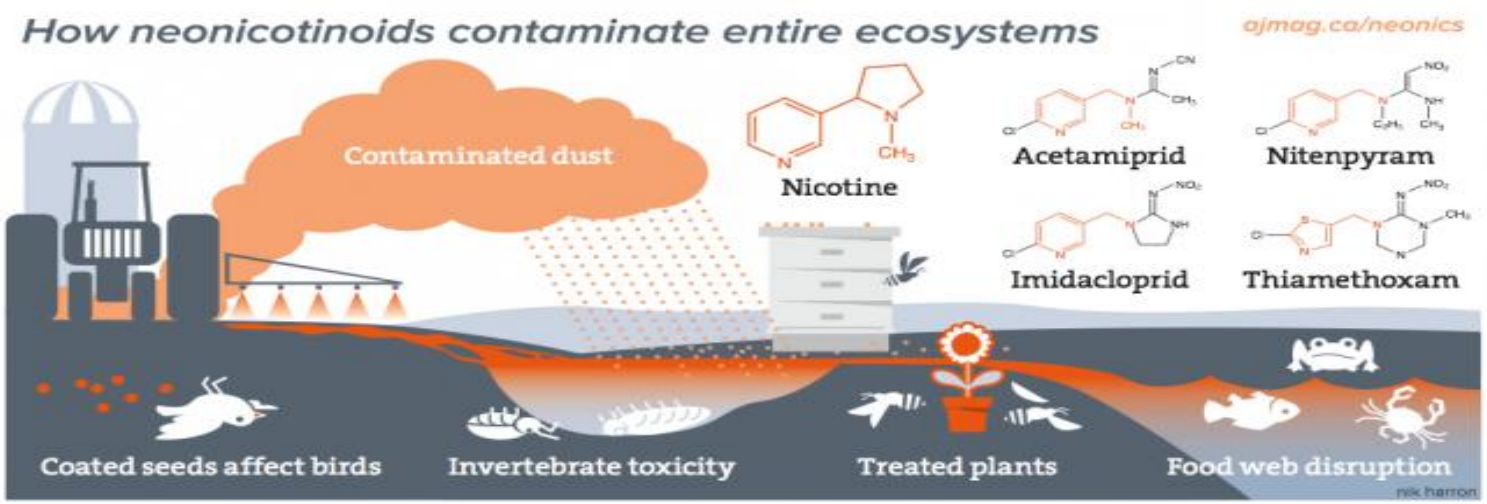
Including industry-sponsored studies

The single most comprehensive study of neonics

Peer reviewed

Published as open access

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

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

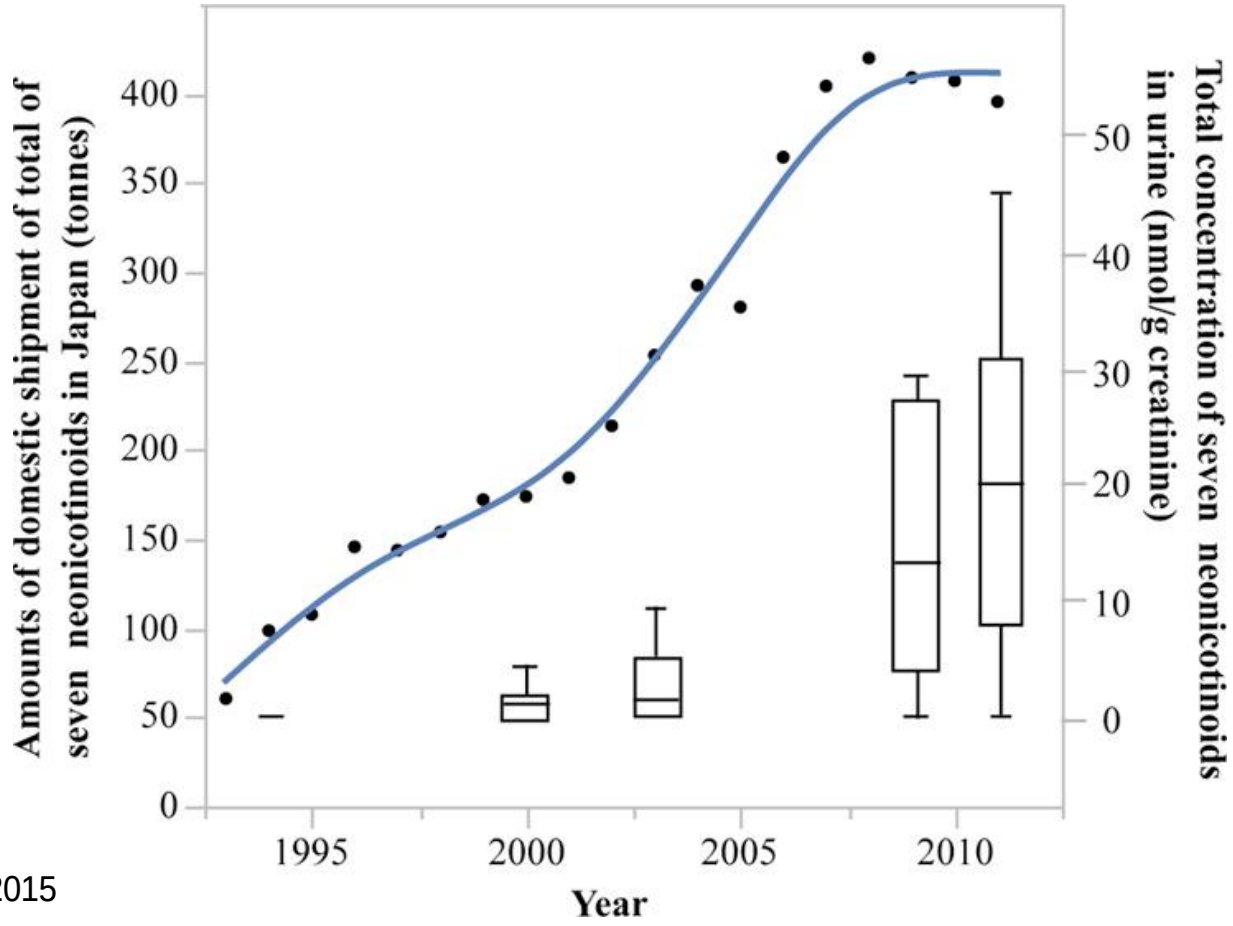
Table 5. Summary of Neonicotinoids Concentrations in Foods

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

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

Chen et al. 2014

Temporal Levels of Urinary Neonicotinoid Concentrations in Japanese Women



Reference: Ueyama 2015

Review of Literature

Are Neonicotinoids Reproductive Toxicants?

Green Screen Evidence Review 2014

Target	Reproductive Toxicity	Endocrine Disruption
Imidicloprid	Moderate	Moderate
Clothianidin	Moderate	Moderate
Thiamethoxam	Moderate	Data Gap

	Objective	Neonicitinoid	Animal	Findings *Indicates Statistically significant result
Najafi (2010)	Evaluate chronic effect of IM exposure on testicular tissue, sperm morphology, and testerone 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)	Evaulate 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 does 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
Rasgele (2014)	Investigate genotoxic effects of ACE on mouse germ cells	Acetamiprid	Male mice	Acm “induced different types of sperm abnormalities e.g., “hookless, banana, amorphous and folded sperms at all concentrations” Acm slightly increased the percentage of abnormal sperm in mouse germ cells
Hirano (2015)	Investigate effect of CTD and	Clothianidin	Male mice	GPx4 immunoreactivity was detected in sperm and diffuse Gpx4 immunoreactivity was seen in permatid

Human Acute exposure findings

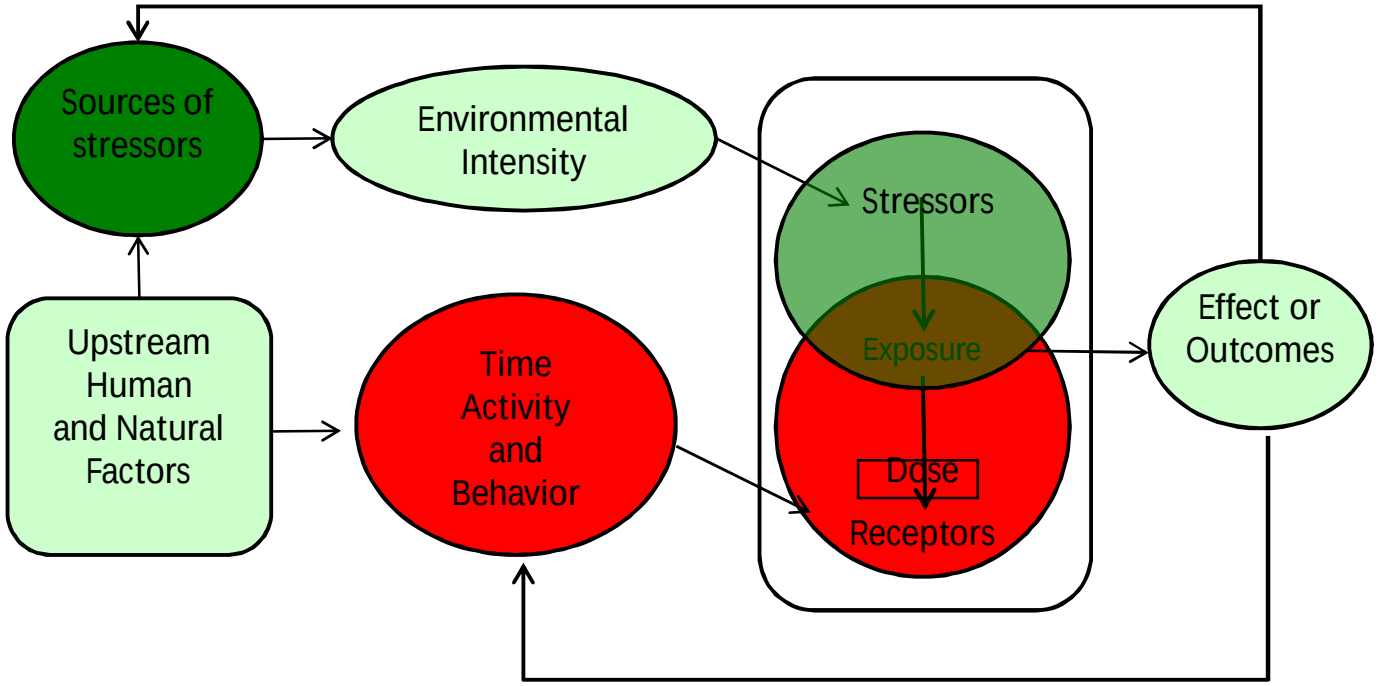
First author (year)	Study population	Country of study	Results
			Acute exposure
Elfman (2009)	19 conifer seedling planters: 17 men, 2 women	Sweden	No clear acute adverse effects reported after 1 week of exposure to IMI-treated seedlings
Forrester (2014)	1142 exposure cases reported to a TX poison control network from 2000-2012	USA	Of the 1142, 77% were identified as IMI alone or in combination with other neonics. 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.
Mohamed (2009)	68 hospital patients: 61 ingestion, 7 dermal exposures	Sri Lanka	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.
Phua (2009)	70 exposure cases reported to the Taiwan National Poison Center	China	Of the 57 cases of ingested neonics, 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%).

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

Author (Year)	Study Population	Country of Study	Results
Carmichael (2014)	101 heart defect cases recruited from mothers who participated in a pop-based case control study in San Joaquin valley; 9 exposed/92 not exposed	USA	Significant association between residential proximity to agricultural use of IMI and tetralogy of Fallot (AOR 2.4, 95% CI: 1.1-5.4)
Keil (2014)	407 children with autism spectrum disorder (ASD) recruited from Childhood Autism Risk from Genetics and Environment (CHARGE) Stuyd/ 206 controls	USA	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
Marfo (2015)	35 symptomatic cases in Gunma prefecture/ 50 controls	Japan	Significant association between urinary DMAP and increased prevalence of memory loss, finger tremor, and other symptoms of unknown origin (OR 14, 95% CI: 3.5-57)
Yang (2014)	73 anencephaly cases in San Joaquin valley; 6 exposed/67 not exposed	USA	Suggestive association between residential proximity to agricultural use of IMI and anencephaly (AOR 2.9, 95% CI: 1.0-8.2)

Source to Effect Framework



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