Testimony by City of Wilsonville Mayor Shawn O'Neil Supporting HB 2679:

Proposed Legislation Restricts Use of Products Containing Powerful Class of Neonicotinoid Pesticides Shown to Be Harmful to Pollinators and Ag Industry

Scheduled for public hearing on March 4, 2025, before the
House Committee On Climate, Energy, and Environment

Chair Lively, Vice-Chairs Gamba and Levy, and Members of the Committee:

I am testifying on behalf of the City of Wilsonville in strong support of HB 2679, which directs the State Department of Agriculture to classify certain pesticides containing neonicotinoids, aka neonics, as restricted-use and prohibit application of restricted-use neonicotinoid pesticides on residential landscapes, subject to certain exceptions.

In June 2013 Wilsonville was the site on private property of reportedly the largest pollinator bumble bee-kill in the history of the US, a distinction that our community does not relish — all due to the application of neonicotinoid pesticides by trained professional applicators. This powerful class of pesticides has been shown conclusively to harm pollinators throughout the life-cycle of the product, with detrimental effects continuing long after initial treatment since plants take-up the pesticide into their tissues.

The two scientific research papers published in 2024 titled "Human acute poisoning incidents associated with neonicotinoid pesticides in the U.S. Incident Data System (IDS) database from 2018–2022" and "Neonicotinoid pesticides: evidence of developmental neurotoxicity from regulatory rodent studies," highlight how the risks of exposure are especially concerning for infants and children, who can ingest neonics through contaminated food, water, and even breast milk.

In 2020, the US EPA issued an advisory to homeowners to not use neonicotinoid products. In 2014, the European Union banned the use of three types of neonicotinoid pesticides in crops that attract bees.

Many local, Wilsonville-area farming and nursery businesses are dependent upon pollinator health for propagation of key nut, fruit and vegetable crops. The Department of Agriculture found that four separate bumble bee-kill incidents in 2013 and three separate bee-kill incidents in 2014 were due to applications of neonicotinoid pesticides by duly licensed pesticide applicators.

The City appreciates your consideration and urges your support of HB 2679.

Shawn O'Neil, Mayor
City of Wilsonville

EXHBITS:

- Environmental Health, 2024, "Human acute poisoning incidents associated with neonicotinoid pesticides in the U.S. Incident Data System (IDS) database from 2018–2022 – frequency and severity show public health risks, regulatory failures"
- Frontiers in Toxicology, 2024, "Neonicotinoid pesticides: evidence of developmental neurotoxicity from regulatory rodent studies"
- Los Angeles Times, Jun 21, 2013, "Pesticide blamed in death of 25,000 bumblebees in Oregon"
- ABC News, Jun 22, 2013, "More Than 25,000 Bees Die in Oregon."
- Time magazine, August 19, 2013, "A World Without Bees: The Price We'll Pay If We Don't Figure Out What's Killing The Honeybee."

Environmental Health

RESEARCH

Open Access

Human acute poisoning incidents associated with neonicotinoid pesticides in the U.S. Incident Data System (IDS) database from 2018–2022 – frequency and severity show public health risks, regulatory failures

Jennifer B. Sass[1*] and Daniel Raichel[2]

Abstract

Background Neonicotinoid pesticides ('neonics') – imidacloprid, thiamethoxam, clothianidin, acetamiprid, dinotefuran—are the most widely used class of insecticides in the world. They have a neurotoxic mechanism of action, similar to nicotine. They are detected in food, waterways, tap water, and breast milk.

Methods We make use of the non-occupational human pesticide poisoning reports in the U.S. Environmental Protection Agency (EPA) online Incident Data System (IDS). The data set contains individual incidents, and incidents aggregated and submitted in bulk to EPA. IDS reports are predominantly self-reported information of varying and often low level of detail and are not routinely validated or verified by EPA.

Results We reviewed 842 non-occupational human poisoning incidents associated with neonics in the IDS from 2018 through 2022. There are four human fatality reports, two associated with clothianidin and two with acetamiprid. Major illnesses such as seizures were reported in several cases, including with dinotefuran cockroach bait product, and an imidacloprid lawn product. Moderate poisonings make up 88% of the total poisonings (740 of 842), with most of those associated with imidacloprid (547 incidents) or dinotefuran (102 incidents). Common reported symptoms classified as moderate often included two or more of the following: headaches; dizziness; lethargy; eye or throat irritation; skin itching and rash; chemical burns and skin peeling; face swelling; muscle weakness or tremors; vomiting; diarrhea; pain and tightness in chest; open sores; and general pain. These incidents stem mainly from residential uses, such as lawn and garden insect repellents, home pest treatments for bed bugs or roaches, and products used to treat pets for fleas and ticks.

Conclusion Given the evidence of neurotoxicity, EPA should use its legal authority to cancel unsafe products and unnecessary uses – including from seed treatments, and residential pet and lawncare products – to prevent further human suffering.

Keywords Neonicotinoid, Neurotoxic, Pesticide, Poisoning, Human, Seizure, Death

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Background

Neonicotinoid pesticides, or "neonics," are the most widely used insecticides in the world, making up roughly one-quarter of global insecticide use [1, 2]. Their popularity is in large part because they are often characterized as posing little to no risk to vertebrates, including humans, due to their much lower affinity for the target receptor in vertebrates, compared with insects [3, 4]. The first neonic manufacturer, Bayer, stated in a 2016 report that, "[t]he toxicity of neonicotinoids to mammals and humans is very low" [5]. The chemicals are similar to nicotine and are toxic by a similar mechanism, acting as an agonist on the nicotinic acetylcholine receptor (nAChR), to overstimulate affective nerve cells and systems [3]. The concerns with neonics have focused on their devastating effects on bees, aquatic invertebrates, and beneficial insects, with good reason, as neonics are thought to be responsible for making agriculture almost fifty times more harmful to insects [6]. In fact, the U.S. Environmental Protection Agency (EPA) predicts that the neonics jeopardize the continued existence of over 200 threatened and endangered species – about 11% of the entire endangered species list – including many bees, butterflies, and other beneficial pollinating insects [7–9].

The class of neonics includes: imidacloprid; thiamethoxam; clothianidin; acetamiprid; dinotefuran. They are registered in over 120 countries, on more than 140 fruit, vegetable, and field crops to target sucking and chewing insects such as aphids or emerald ash borers [10]. The EPA has approved over 1,000 products containing neonics, including for agricultural crops, urban landscaping, and indoor bed bug and flea and tick treatments for pets.

Since neonics persist in soil and are highly water soluble, both the agricultural and consumer uses of neonic products contaminate soil and water. A national stream sample report by the U.S. Geological Survey found that clothianidin and thiamethoxam detections in surface water were related to uses on crops, whereas imidacloprid was the most frequently detected neonic in urban stream samples (37% of samples), with concentrations related to use on lawns, gardens, parks, and playgrounds [11]. A study in Minnesota reported a similar pattern, with the highest neonic detections associated with agricultural use, mainly clothianidin, followed by neonics use in urban areas, mainly imidacloprid, suggesting that both agriculture and urban uses contribute to chronic exposure [12]. Neonics have also been reported in tap water and foods including fruits, vegetables and baby foods, and human breast milk [13–17].

Here we provide a summary and discussion of the publicly available neonicotinoid human poisoning reports in EPA's IDS over five years, from 2018–2022.

Methods

As of July 2023, EPA made 10 years of pesticide incident data available on its online IDS database [18]. The IDS is a national database, populated with human health information from several sources, largely from pesticide manufacturers (called "registrants"), which are required to notify EPA of "information regarding unreasonable adverse effects on the environment of the pesticides" they register, including occupational, residential and ecological incidents [19]. Additional submissions come from State agencies, National Poison Centers, and the National Pesticide Information Center (NPIC), as well as individual reports to the database from pesticide applicators, agriculture workers, homeowners or tenants, health care professionals, and the general public [20]. IDS reports are predominantly self-reported information of varying and often low level of detail around exposure circumstances, symptoms, and/or medical outcome. The information is not routinely validated or verified by EPA, though reports from poison control centers and some states may be confirmed [21]. See EPA's website for details including data limitations [22].

While ecological incidents are also included in IDS, we did not analyze these data. Our data analysis excludes any other databases or data sources, so as to avoid potential for double counting the same cases reported to multiple entities. For example, the NPIC shares some incident reports with IDS, roughly five-to-ten reports each month.

While IDS contains some occupational incidents, most occupational poisonings are reported to two other databases. The California Pesticide Illness Surveillance Program (PISP) includes physician-reported pesticide worker poisonings for the state of California. The Sentinel Event Notification System for Occupational Risk (SENSOR) is a national database that aggregates reports from states, physicians, emergency room records, workers' compensation claims, and Poison Control Centers. Neither PISP nor SENSOR are incorporated into the IDS. Since most of the occupational incidents that EPA uses come from PISP or SENSOR, with many fewer coming through IDS, by limiting the source of poisoning incidents to just the EPA's IDS, occupational incidents are largely excluded from this analysis. For those readers interested in occupational exposures, we direct them to the National Institute for Occupational Safety and Health (NIOSH) which compiles data from the SENSOR-Pesticides Program and the National Poison Data System and reports the findings in its Pesticide Illness and Injury Surveillance Program [23].

To avoid double-counting within the IDS data, we scrutinized each line-entry individually, excluding duplicate poisoning cases reported on multiple line-entries. We also excluded any reports not reasonably attributable to

pesticide exposure, such as one report of an injury from a 'plane crash,' presumably during crop dusting activities. Intentional pesticide ingestion cases were also excluded since they do not represent the intended use of the product. However, we included poisoning reports where the product was used as intended, but possibly not as per label directions, for example: poisonings from a splash or spill while using the product; exposure due to improper ventilation; or premature re-entry into a pesticide-treated area in conflict with label instructions. We included these reports because they represent the real-world use and injury patterns associated with these products.

Results

Over a five-year period from 2018 through 2022, U.S. EPA received reports of just over 840 people poisoned with neonics; these values should be considered estimates given the lack of individual details in the data reports [24]. Incidents included symptoms ranging from human fatalities (H-A) to major (H-B), moderate (H-C), or minor (H–D) injuries [25]. Imidacloprid was implicated in roughly 70% of the total individual poisonings, most with moderate symptoms of poisoning. See Table 1 for the tabulations of the number of human poisoning incidents by severity and by individual neonic pesticide.

See Table 2 for the list of 56 human incidents between 2018 and 2022 that include reports classified as H-A or H-B. On July 11, 2023, we submitted a request to EPA under the Freedom of Information Act for the full incident reports for each of the 56 cases, along with any records such as correspondence, meeting minutes, memoranda, and emails associated with the 56 cases. On October 28, 2024 we received redacted reports responsive to our request. Below we provide additional details for the four human fatality cases from the full reports.

The EPA incident reports include four human fatality reports, two associated with clothianidin and two with acetamiprid. For the two clothianidin associated fatalities, EPA states only that in 2019, "2 people died involving Crossfire Bed Bug treatment [25]" (See Table 2). The two acetamiprid fatalities were from 2018: an entry for "Ortho Flower, Fruit and Vegetable Insect Killer Ready-To-Use" with a hand wand applicator reported that "[s]ymptoms include sudden death;" another for "transport termicide [sic] insecticide" reported that, "a man in poor health died after a pesticide application in Sect. 8 apartments [25]" (See Table 2).

The full reports we received from EPA in response to our follow-up FOIA request including the following additional information about the above reported fatalities:

> EPA Report #0322022-00001 - On 07/28/2017 Certified completed a Heat treatment and used crossfire (clothianidin). Product used: Crossfire Bed Bug Concentrate; Reg. No. 1021-2776. A tenant's daughter was told repeatedly they could not enter the unit. When the tech was finishd and loading equipment he allowed her to enter for meds. She exited and he told

Table 1 Tabulation of Entries in the U.S. EPA Incident Data System of human pesticide poisoning incidents associated with neonicotinoid insecticides over a 60-month period from 2018 through 2022

IDS Data 2018-2022 (60 months)	Human fatality (HA)	Human major (HB)	Human moderate (HC)	Human minor (HD)	TOTAL by chemical	General Observations
Clothianidin	2	7	46	0	55	HA involving Crossfire Bed Bug treatment. HB/C mainly crop uses, some from dust from treated seeds, feed store worker spilled bag of treated seeds
Dinotefuran	0	13	102	5	120	HB mainly roach and ant gel bait. HC mainly during application of dog products
Thiamethoxam	0	1	39	2	42	HC mainly agriculture products
Acetamiprid	2	1	6	10	19	HA sudden deaths reported with home garden product. HB, seizure, tinnitus, 2 miscarriages reported with home garden product
Imidacloprid	0	51	547	8	606	HB/C mainly pet products, some soil and turf products. HB seizures, intracranial bleeding, premature birth. HC vomiting, chemical burns. HD mainly diarrhea (excluded HA plane crash and intentional suicide
TOTAL by severity	4	73	740	25	842	

Each incident represents an individual person; these values should be considered rough estimates given the lack of individual details in the data reports. The severity of the injury is reported as it was reported in the EPA database except in 3 cases for which a seizure was reported, but the incident was classified as H-C (moderate) and which here is classified as H-B (major) consistent with EPA ratings

Table 2 IDS entries that include H-A and/or H-B incidents associated with neonicotinoid pesticides, 2018-2022

	Author's notes	Package and Report #	Package Description	Submitter	Inc. Date	Exp. Sev. Code	Ingredient Name	Product Name	Registrant	H-A	H-B
1		032022-00001	MGK: Includes 1 H-A. 2 people died involving Crossfire Bed Bug treatment. (JK)	MCLAUGHLIN GORMLEY KING CO.	04/17/2019	HA	Clothianidin	CROSSFIRE BED BUG CONCENTRATE	MCLAUGHLIN GORMLEY KING COMPANY	2	
2		031616-00001	Scotts: Includes 1 H-A. Symptoms include Sudden death. (JK)	SCOTTS CO. LLC	11/21/2018	HA	Acetamiprid	ORTHO FLOWER, FRUIT & VEGETABLE INSECT KILLER READY TO USE WAND	NIPPON SODA CO., LTD.	1	
3		031700-00004	Nisso: Dec. 2018, a man in poor health died after a pesticide application in Section 8 apartments.	NISSO AMERICA, INC. FOR NIPPON SODA CO., LTD.	07/01/2018	HA	Acetamiprid	TRANSPORT TERMICIDE INSECTICIDE	NIPPON SODA CO., LTD.	1	
46		034402-00001	Nisso: Includes 1 H-B. Symptoms include numbness/tingling and dermal irritation/pain. (JK)	NISSO AMERICA, INC. FOR NIPPON SODA CO., LTD.	06/04/2021	HB	Acetamiprid	TRANSPORT (R) MIKRON INSECTICIDE	NIPPON SODA CO., LTD.		1
12		033054-00005	MGK: Includes 2 H-B (-002&-005) and 3 H-C. Symptoms include Emesis, Cough, Wheezing, etc. (JK)	MCLAUGHLIN GORMLEY KING CO.	12/30/2019	HB	Clothianidin	RAID BED BUG FOAMING SPRAY	MCLAUGHLIN GORMLEY KING COMPANY, D/B/A MGK		2
15		034505-00019	SC Johnson: 2 H-B(-004,-009) and 19 H-C. Symptoms include edema, pruritus, ocular irritation, etc. (JK)	SC JOHNSON	08/27/2021	HC	Clothianidin	RAID BED BUG FOAMING SPRAY	MCLAUGHLIN GORMLEY KING COMPANY, D/B/A MGK		2
25		031675-00004	MGK: Includes 7 H-C and 1 H-B (-008). Symptoms include Diarrhea, IBS, Emesis/Vomiting, etc. (JK)	MCLAUGHLIN GORMLEY KING CO.	09/26/2018	HC	Clothianidin	CROSSFIRE BED BUG	MCLAUGHLIN GORMLEY KING COMPANY		1
26		031739-00001	MGK: Includes 1 H-B (-004) and 4 H-C. Symptoms include Palpitation, Dyspnea/Shortness of Breath, Wheezing, etc. (JK)	MCLAUGHLIN GORMLEY KING CO.	01/01/2018	HC	Clothianidin	CROSSFIRE AEROSOL	MCLAUGHLIN GORMLEY KING COMPANY		1
27		032081-00002	MGK: Include 1 H-C and 1 H-B (-002). Symptoms include Urinary trac infection, Ataxia, Headache, etc. (JK)	MCLAUGHLIN GORMLEY KING CO.	03/22/2019	HB	Clothianidin	CROSSFIRE	MCLAUGHLIN GORMLEY KING COMPANY		1
5		033563-00002	United Industries: Includes 4 H-B (-005,-007,-009,-013) and 13 H-C. Symptoms include pruritus, hives, dermal irritation, etc. (JK)	UNITED INDUSTRIES CORP.	08/11/2020	HC	Dinotefuran	HOT SHOT ULTRA LIQUID ROACH BAIT	CHEMSICO		4
6		032335-00019	United: Includes 3 H-B(-001,-005&-015), 15 H-C and 5 E-A. Symptoms include Ataxia, Dizzy/Vertigo, Syncope, etc. (JK)	UNITED INDUSTRIES CORP.	06/20/2019	HC	Dinotefuran	HOT SHOT ULTRA LIQUID ANT BAIT	CHEMSICO		3
13		033155-00007	United industries: Includes 2 H-B(-001,-004) and 5 H-C. Symptoms include Asthma, Cough, Chock, etc. (JK)	UNITED INDUSTRIES CORP.	03/30/2020	HC	Dinotefuran	HOT SHOT ULTRA LIQUID ROACH BAIT	CHEMSICO		2
14		033477-00006	United Industries: Includes 2 H-B(-004&-006),19 H-C, and 3 E-A. Symptoms include laceration, bleed, numbness, etc. (JK)	UNITED INDUSTRIES CORP.	07/08/2020	HB	Dinotefuran	HOT SHOT ULTRA LIQUID ANT BAIT	CHEMSICO		2
20	incl seizure, should be H-B	031035-00001	BASF: Includes 1 H-C. Symptoms include seizure.	BASF CORP.	03/12/2018	HC	Dinotefuran	PRESCRIPTION TREATMENT BRAND ALPINE COCKROACH GEL BAIT RESERVOIR	BASF CORPORATION		1
36		033110-00001	Ceva: Includes 1 H-B. Symptoms include Anaphylactic Shock, Throat irritation and Erythema at the exposure site. (JK)	CEVA ANIMAL HEALTH, LLC	03/13/2020	HB	Dinotefuran	CATEGO FOR CATS	CEVA ANIMAL HEALTH, LLC		1
4		031139-00026	Bayer: Includes 21 H-C and 5 H-B. Symptoms include paraesthesia, oedema, skin change, etc.	BAYER HEALTHCARE, ANIMAL HEALTH, INC.	05/29/2018	HC	Imidacloprid	SERESTO DOG (UNSPECIFIED)	BAYER HEALTHCARE LLC		5
7		030787-00014	Bayer Animal Health: Includes 1 D-D, 11 H-C and 2 H-B. Symptoms include Hypersalivation, Paraesthesia, Hypersensitivity reaction, etc. The updates in this report are nowhere found in the system so some of the updates as a source could not be added.	BAYER HEALTHCARE, ANIMAL HEALTH, INC.	01/19/2018	HC	Imidacloprid	SERESTO SMALL DOG	BAYER HEALTHCARE LLC		2
8		030880-00007	Bayer: includes 6 H-C and 2 H-B. Symptoms include Taste disorder, Headache, Nausea, etc.	BAYER HEALTHCARE, ANIMAL HEALTH, INC.	02/23/2018	HC	Imidacloprid	ADVANTAGE II (CAT-UNSPECIFIED)			2
9		031131-00005	Bayer: Includes 8 H-C, 2 H-B and 4 P-A. Symptoms include Light headness, Shortness of breath, Edema/Swelling, etc.	BAYER CROPSCIENCE	05/15/2018	HB	Imidacloprid	CORETECT TREE AND SHRUB TABLETS	BAYER ENVIRONMENTAL SCIENCE		2
10		032379-00004	MGK:Includes 2 H-B(-001&-004) and 4 H-C. Symptoms include Malaise, Cough, Emesis/Vomiting, etc. (JK)	MCLAUGHLIN GORMLEY KING CO.	06/15/2019	HB	Imidacloprid	BEDLAM PLUS	MCLAUGHLIN GORMLEY KING COMPANY		2
11		033023-00005	Bayer: Includes 2 H-B(-001&-002) and 4 H-C. Symptoms include Hair loss, Numbness, Joint pain, etc. (JK)	BAYER CROPSCIENCE LP	01/30/2020	HC	Imidacloprid	TEMPRID FX	BAYER ENVIRONMENTAL SCIENCE		2
16		034640-00001	Elanco: Includes 2 H-B. Symptoms include headache, hypoaesthesia, dyspnea, etc. (JK)	ELANCO US INC.	10/06/2021	HB	Imidacloprid	SERESTO COLLAR UNKNOWN	ELANCO US INC.		2
17		034640-00002	Elanco: Includes 2 H-B. Symptoms include headache, hypoaesthesia, dyspnea, etc. (JK)	ELANCO US INC.	08/01/2021	HB	Imidacloprid	SERESTO LARGE DOG	ELANCO US INC.		2
18		030702-00009	Bayer: Includes 9 H-C and 1 H-B. Symptoms include Dermatitis, Eczema, Paraesthesia, etc.	BAYER HEALTHCARE, ANIMAL HEALTH, INC.	01/06/2018	HC	Imidacloprid	ADVANTAGE II MEDIUM DOGS	BAYER HEALTHCARE LLC		1
19		030942-00011	Bayer: Mar 2018, 11 human incidents due to pet products, 1 H-B.	BAYER HEALTHCARE, ANIMAL HEALTH, INC.	03/05/2018	HC	Imidacloprid	SERESTO LARGE DOG	BAYER HEALTHCARE LLC		1
21	excluded 1 H-C for potential report mistake	031076-00008	Bayer: Includes 5 H-C, 1 H-B (-008) and 2 P-A. Symptoms include Rash, Confusion, Dizziness/Vertigo, etc. (JK) (For -006, source 031076-0001 was put by mistake. Please ignore.)	BAYER ENVIRONMENTAL SCIENCE	05/07/2018	HB	Imidacloprid	TEMPRID SC INSECTICIDE	BAYER ENVIRONMENTAL SCIENCE		1
22		031207-00003	Scotts: Includes 16 H-C, 10 P-A, 1 W-A (-133), 1 H-B (-204) and 186 P-L. Symptoms include Palpitation, Dizziness, Chest Pain, etc. (JK)	SCOTTS CO. LLC	05/31/2018	HC	Imidacloprid	HOME DEFENSE DUAL-ACTION BED BUG KILLER AEROSOL	MCLAUGHLIN GORMLEY KING COMPANY		1
23		031232-00021	Bayer Animal Health: Includes 1 H-B and 20 H-C. Symptoms include Pruritus, Erythema, Diarrhea, etc.	BAYER HEALTHCARE, ANIMAL HEALTH, INC.	07/01/2018	HC	Imidacloprid	K9 ADVANTIX II (UNSPECIFIED)			1
24		031321-00002	Bayer: Includes 1 H-B and 1 H-C. Symptoms include Hypoaesthesia, Paraesthesia, Peripheral nervous system disorder, etc. (JK)	BAYER HEALTHCARE, ANIMAL HEALTH, INC.	05/28/2018	HC	Imidacloprid	SERESTO CAT	BAYER HEALTHCARE LLC		1
28		032218-00006	Bayer: include 5 H-C and 1 H-B(-006). Symptoms include Dysphagia, Alopecia, Weight loss, etc. (JK)	BAYER HEALTHCARE, ANIMAL HEALTH, INC.	05/01/2018	HB	Imidacloprid	QUICKBAYT FLY BAIT (UNSPECIFIED)	BAYER HEALTHCARE LLC		1
30		032439-00002	Bayer: Includes 2 H-C, 1 H-B(-002) and 25 P-A. Symptoms include Nausea Emesis/Vomiting, Cough, etc. (JK)	BAYER CROPSCIENCE LP	07/15/2019	HB	Imidacloprid	TEMPRID SC INSECTICIDE	BAYER ENVIRONMENTAL SCIENCE		1
31		032465-00002	Bayer: Includes 4 H-C, 1 H-B(-002) and 25 P-A. Symptoms include Oral irritation, throat irritation, Dizziness/Vertigo, etc. (JK)	BAYER CROPSCIENCE LP	07/17/2019	HB	Imidacloprid	TEMPRID SC INSECTICIDE	BAYER ENVIRONMENTAL SCIENCE		1
32		032593-00004	Bayer: Includes 1 H-B (-001) and 3 H-C. Symptoms include Hypoaesthesia, Central nervous system disorder, Multiple sclerosis, etc. (JK)	BAYER HEALTHCARE, ANIMAL HEALTH, INC.	04/27/2019	HC	Imidacloprid	SERESTO CAT	BAYER HEALTHCARE LLC		1
33		032706-00005	Bayer: Include 4 H-C, 1 H-B(-005), 2 P-A and 3 P-B. Symptoms include Abdominal Pain, Confusion, Dizziness, etc. (JK)	BAYER CROPSCIENCE LP	10/09/2019	HB	Imidacloprid	TEMPRID SC INSECTICIDE	BAYER ENVIRONMENTAL SCIENCE		1
34		032808-00002	Bayer: Includes 1 H-B(-001), 2 H-C and 1 P-A. Symptoms include Hypotension, Blood clot in right hand, Skin discoloration, etc. (JK)	BAYER CROPSCIENCE LP	10/01/2019	HC	Imidacloprid	TEMPRID SC INSECTICIDE	BAYER ENVIRONMENTAL SCIENCE		1
35		033013-00073	Scotts: 72 aggregate summaries. October - December, 2019. Includes 1 H-B(-082), 4 H-C and 8 P-L. Symptoms include Erythema, Hives/Welts, Dermal Irritation, etc. (JK)	SCOTTS CO. LLC	01/05/2020	HC	Imidacloprid	HOME DEFENSE DUAL-ACTION BED BUG KILLER AEROSOL	MCLAUGHLIN GORMLEY KING COMPANY, D/B/A MGK		1
37		033203-00003	SBM: Includes 1 H-B(-002) and 2 H-C. Symptoms include Dyspnea, Emesis, Seizure, etc. (JK)	SBM LIFE SCIENCE CORP.	04/17/2020	HC	Imidacloprid	BIOADVANCED COMPLETE INSECT KILLER FOR SOIL AND TURF READY-TO-SPRAY	SBM LIFE SCIENCE CORP.		1
38		033386-00221	Scotts: Includes 1 H-B(-001), 6 H-C, 1 D-E, 13 P-A, 1 D-A and 231 P-L. Symptoms include bronchospasm, congestion, diarrhea, etc. (JK)	SCOTTS CO. LLC	06/25/2020	DA	Imidacloprid	HOME DEFENSE MAX BED BUG, FLEA & TICK KILLER	THE SCOTTS COMPANY		1
39		033567-00008	Bayer: Includes 9 P-A, 1 H-B(-008), 7 H-C, 1 H-D, 1 D-A, 1 D-B and 4 P-L. Symptoms include pruritus, rash, blisters, etc. (JK)	BAYER CROPSCIENCE LP	05/01/2020	HB	Imidacloprid	TEMPRID FX INSECTICIDE	BAYER ENVIRONMENTAL SCIENCE		1
40		033624-00005	Bayer: Includes 1 H-B (-003), 7 H-C, 4 H-D, 3 P-A, 2 P-B and 2 P-L. Symptoms include dermal irritation, edema, tingling, etc. (JK)	BAYER CROPSCIENCE LP	09/25/2020	HC	Imidacloprid	TEMPRID SC INSECTICIDE	BAYER ENVIRONMENTAL SCIENCE		1
41		033894-00001	Bayer: Includes 1 H-B(-001) and 1 H-C. Symptoms include tachycardia, ataxia, confusion, etc. (JK)	MONSANTO CO./BAYER CROP SCIENCE	01/01/2021	HB	Imidacloprid	TEMPRID FX INSECTICIDE	BAYER ENVIRONMENTAL SCIENCE		1
42		033918-00022	Elanco: May 2020 thru January 2021 individual reports. Includes 1 H-B(-021) and 21 H-C. (JK)	ELANCO ANIMAL HEALTH, A DIV. OF ELI LILLY AND CO.	12/06/2020	HC	Imidacloprid	ADVANTAGE II MEDIUM DOG	ELANCO US INC.		1
43		033997-00005	Bayer: Include 1 H-B(-005) and 4 H-C. symptoms include Joint pain, cough, nose bleed, etc. (JK)	MONSANTO CO./BAYER CROP SCIENCE	09/01/2020	HB	Imidacloprid	TEMPRID FX INSECTICIDE	BAYER ENVIRONMENTAL SCIENCE		1
44	incl seizure, should be H-B	034040-00001	Elanco: Includes 19 H-C. Symptoms include convulsion, seizure, hemorrhage, etc. (JK)	ELANCO US INC.	01/01/2021	HC	Imidacloprid	SERESTO DOG (UNSPECIFIED)	ELANCO US INC.		1
45		034220-00001	Elanco: Includes 1 H-B(-003) and 8 H-C. Symptoms include muscle tremor, dyskinesia, urticaria, etc. (JK)	ELANCO US INC.	03/31/2021	HC	Imidacloprid	ADVANTAGE II EXTRA LARGE DOG	ELANCO US INC.		1
47		034567-00002	Elanco: Includes 1 H-C and 1 H-B(-002). Symptoms include headache, weight loss, emesis, etc. (JK)	ELANCO US INC.	07/01/2021	HB	Imidacloprid	SERESTO LARGE DOG	ELANCO US INC.		1
48		034587-00005	Bayer: Includes 1 H-B(-001), 4 H-C and 4 P-L. Symptoms include edema, coughing up blood, dyspnea, etc. (JK)	MONSANTO CO./BAYER CROP SCIENCE	08/24/2021	HC	Imidacloprid	TEMPRID SC INSECTICIDE (CANADA PMRA# 32524)	BAYER ENVIRONMENTAL SCIENCE		1
49		034712-00001	RD: Includes 1 H-B. Seresto incident. (JK)	U.S. EPA, OPP, RD	12/16/2021	DB	Imidacloprid	SERESTO	ELANCO US INC.		1
50		034772-00001	Elanco: Includes 1 H-B. Symptoms include pruritus and dyspnoea.	ELANCO US INC.	12/01/2021	HB	Imidacloprid	SERESTO CAT	ELANCO US INC.		1
51		034880-00001	Elanco: Includes 1 H-B and D-A. Symptoms of child include convulsion. (JK)	ELANCO US INC.	01/31/2019	HB, DA	Imidacloprid	SERESTO LARGE DOG	ELANCO US INC.		1
52	incl seizure, should be H-B	034921-00001	FMC: Includes 1 H-C. Symptoms include blotchy & red fac, seizure, pass out. (JK)	FMC CORPORATION	02/23/2022	HC	Imidacloprid	TRIPLE CROWN T&O INSECTICIDE	FMC CORPORATION		1
53		035279-00003	Scotts: Includes 1 H-B(-002), 5 H-C, 6 P-A and 77 P-L. Symptoms include nauseous, dizzy, chest congestion, etc. (JK)	SCOTTS CO. LLC	05/25/2022	HC	Imidacloprid	ORTHO HOME DEFENSE BED BUG, FLEA & TICK KILLER SPRAY	MCLAUGHLIN GORMLEY KING COMPANY, D/B/A MGK		1
54		035375-00002	Bayer: Includes 1 H-B(001), 8 H-C, 2 P-L and 9 P-A. Symptoms include burning skin, stomach cramps, postules on bodies, etc. (JK)	MONSANTO CO./BAYER CROP SCIENCE	04/01/2022	HC	Imidacloprid	PREMISE FOAM	BAYER ENVIRONMENTAL SCIENCE		1
55		035389-00002	SBM: Includes 1 H-B(-003) and 3H-C. Symptoms include bullae, erythema, burn, etc. (JK)	SBM LIFE SCIENCE CORP.	08/17/2022	HC	Imidacloprid	BIOADVANCED - 3 IN 1 INSECT, DISEASE & MITE CONTROL READY-TO-SPRAY	SBM LIFE SCIENCE CORP.		1
56		035646-00002	Elanco: Includes 1 H-B(-002), 1 H-C and 1 H-D. Symptoms include arthritis, neoplasia, urticaria, etc. (JK)	ELANCO US INC.	12/01/2022	HB	Imidacloprid	SERESTO COLLAR UNKNOWN	ELANCO US INC.		1
29		032424-00001	Region 9: Jul7 2019, Monterey County Agricultural Commissioner's (CAC) office was notified of this incident by DPR's Worker Health and Safety branch's PISP (Pesticide Incident Surveillance Program) unit on Thursday, July 25th. They interviewed the 33 year old male that same day from his hospital room. Monterey CAC has also interviewed the five (5) other irrigators and their foreman, as of July 26th. Four of the other irrigators experienced pesticide related symptoms, three of them during that workday and the fourth one that following Monday. Monterey CAC staff is currently working on interviews, PUR data, wind data, evaluating training records, and medical records. This investigation is currently ongoing.	U.S. EPA, REGION 9	07/20/2019	HB, HC	Thiamethoxam	ENDIGO ZC			1

Complete unedited information as provided to the authors by EPA of the IDS database entries of H-A and/or H-B incidents associated with neonicotinoid insecticides over a 60-month period from 2018 through 2022

her again that they could not enter. 15 minutes after the tech left, she took the tenants into the unit. A neighbor discovered 1 deceased and 1 unconscious. The name of the deceased was[redacted] The name of the unconscious person who dies several months later was [redacted]. age unknown. Applier said the complex settled. The prosecuting lawyer is saying something about crossfire could have caused/contributed to the death.

EPA Report #031616-00001 - Ortho flower fruit and vegetable insect killer ready to use wand (acetamiprid). Consumer asked if it was safe to use this product while an elderly person with kidney failure, heart failure, Parkinson's disease and gray's disease, is in the area. I told her we do not recommend that, and people and pets should remain out of the area until it is dry, but once it's dry it's safe. She asked if any of this information was on the label and I read her the precautionary statement on the label. She then went on to say that her mother, who had all of the above mentioned medical conditions, was dead, and that her sister had ben spraying this with her mother in the area and that she (the consumer, caller) did not know about it. She said her daughter was also hospitalized. She seems to be trying to gather evidence to show her sister, I'm not sure. She is not coplaining to us about our product, the whole conversation is about what you can and can't do with the product and what her sister did do with the product.

EPA Report #031700-00004 – Transport Termicide Insecticide (acetamiprid). Caller states that he management has been spraying Transport Termiticide since may in her senior facility and multiple people have had symptoms Caller states that they have been spraying for a bed bug infestation in her building - Respiratory issues and headache for at least a dozen people Two people have been taken by ambulance and one person has passed away... "The management of this building is trying to threaten and harass me because I am asking questions and trying get vulnerable residents with health issues to understand what the SDS [Safety Data Sheet] sheets are for and to read them. They are using in the Senior Building" .... This weekend a man dropped dead in the back of the building. (It is not known what he died from) One person taking in away via EMS [emergency medical service] on Tuesday - that person had COPD [Chronic obstructive pulmonary disease] and on [oxygen]. It had gotten so bad that she could not breathe anymore. She does know this person. Someone else she does not know was taken in an ambulance day before yesterday. She does not know what happened to

> the two men. She is the only advocate in the building. She was a senior care giver at one point. She does not personally have a medical concern to be evaluated. Caller would like Information: Her call was to ask if they are supposed to be getting notices and times of sprays that happen in enclosed hallways with no ventilation. They have been spraying weekly since May in the common areas/hallways. Weekly. Many of the apartments have been sprayed but do not know which ones as they will not tell them. She was told by management that do not have to tell them the times and the dates. They have been getting notices off an on due to the mayor of the town being involved to push to get notices. The Dept of Hazmat [Hazardous Materials] has pushed for notices. The County Health Dept has pushed for notices. The head of the management has said that these chemicals are "non toxic" and put it in writing. …. What kinds of notice should people be getting of spraying? They are not giving information about covering food prep areas. Sometimes they say to get out of the building for 4 hours and sometimes they say you can stay in. She watches for the chemical truck to come around. They do not give notice so a lot of people are walking into the spraying. Since this has been going on since May people are having health side effects. There are 50 plus apartments in the building and the residents are seniors, and … have COPD.

For nonfatal exposures, the overwhelming majority of them are classified as "moderate" severity (H-C). Moderate poisonings make up 88% of the total poisonings (740 of 842), with most of those associated with imidacloprid (547 incidents) or dinotefuran (102 incidents). Common reported symptoms classified as moderate often included two or more of the following: headaches; dizziness; lethargy; eye or throat irritation; skin itching and rash; chemical burns and skin peeling; face swelling; muscle weakness or tremors; vomiting; diarrhea; pain and tightness in chest; open sores; and general pain (See Table 2).

The nonfatal reported incidents stem mainly from residential uses, such as lawn and garden insect repellents, home pest treatments for bed bugs or roaches, and products used to treat pets for fleas and ticks. In many cases, the person who was poisoned was the person applying the pesticide product. In others, the poisoned individuals were exposed after the product was applied by someone else. For example, in 2018 a family of five (two adults and three children) reported symptoms that included skin rashes, vomiting and dizziness (classified as minor symptoms, H–D) upon returning to their apartment after it was treated with a dinotefuran product. The family did not seek medical attention, according to incident reported [25] (See Table 2).

In some cases, agricultural uses resulted in exposures to non-occupational bystanders. For example, in 2019, a school bus with open windows carrying twenty-nine students was "allegedly drifted on by an air blast sprayer making an application" of an acetamiprid product to a citrus orchard [26]. The bus driver and nine students reported having irritated eyes and skin, nausea and headaches (classified as minor symptoms, H–D).

Other reported symptoms included dizziness, irregular heartbeat, chemical burns, diarrhea, nausea and vomiting, and seizures. It is unclear how each of these are classified – whether as major (H-B), moderate (H-C), or minor (H–D) – since a single line report usually consisted of an aggregate of the number of individuals in each category, sometimes followed by a list of symptoms, but without clarifying which symptoms are associated with which category. For example, a report from 2018 simply states, "Bayer: Includes 21 H-C and 5 H-B. Symptoms include paraesthesia, oedema, skin change, etc.," without any indication of how many people and from which category had suffered which symptoms [27]. In another example, a report from 2020 simply says, "United Industries: Includes 2 H-B (-004&-006), 19 H-C…. Symptoms include laceration, bleed, numbness, etc. [28]". For this reason, we provide a summary of the numbers of individuals in each category, but are unable to include their respective symptoms.

We changed the classification in only three cases. In each of these, seizures were reported, which we re-classified from moderate (H-C) to major symptoms (H-B). One, a 2018 entry for a dinotefuran cockroach bait product, reported, "BASF: Includes 1 H-C. Symptoms include seizure [29]". Another 2021 entry from an imidacloprid pet product reported, "Elanco: Includes 19 H-C. Symptoms include convulsion, seizure, hemorrhage, etc." It is unknown what additional symptoms the "etc." may refer to, or how many of the nineteen individuals had which of the symptoms listed. In this case, we re-classified the report as one H-B individual since there was at least one seizure, and eighteen H-C individuals. The third case was in 2022 by FMC Corporation associated with an imidacloprid lawn product that reported, "FMC: Includes 1 H-C. Symptoms include blotchy & red face, seizure, pass out" (See Table 2) [30]. All other reports we reviewed in the database of convulsions or seizures were already classified the symptoms as major (H-B).

Discussion

Over a five-year period from 2018 through 2022, U.S. EPA received reports of roughly 840 people poisoned with neonics, made public in its IDS national database of incident reports from pesticide manufacturers, individuals, poison control centers, states, and various agencies. Most entries are self-reported and vary in detail regarding exposure, symptoms, and outcomes. While the severity and frequency of the acute pesticide poisoning reports associated with the neonic insecticides are surprisingly high, they are likely to be underreported for many reasons, including not knowing how to report an incident, not going to the hospital or health care facility, many treating physicians are not trained to recognize the signs and symptoms of pesticide poisoning, and, that the person poisoned may not know why they are feeling ill or what product they may have been exposed to [31, 32]. An additional reason for potential underreporting, is that we have excluded multiple data sources on neonic poisoning in an effort to avoid potential double-counting of cases, so the data set here will miss incidents that are not included in IDS database.

In 2021, the Midwest Center for Investigative Reporting reported in USA Today on poisonings from pesticides leaching from flea and tick collars, particularly one brand that contains 10% imidacloprid (a neonic) and 4.5% flumethrin (a pyrethroid insecticide). The reports included around 1,700 pet deaths and just under 1,000 people being poisoned. Unfortunately, the EPA re-confirmed its approval of the collars without any formulation changes, though it did require additional label warnings to report potential poisoning incidents [33]. However, an investigation by the EPA's independent Office of Inspector General reported that EPA staff repeatedly raised concerns about the poisonings that were ignored by both EPA management and the pesticide product manufacturer [34].

While acute illness is more likely to be reported because of the rapid onset of symptoms, it may be that low level chronic exposures to neonics during early life neurodevelopment may be even more problematic [35]. A systematic review of epidemiologic studies of neonic exposure in the general population identified a small but statistically significant association with neonic exposure during pregnancy and adverse developmental or neurological impairments including the following (with citations to the original studies): teratology of Fallot [36], anencephaly [37], autism spectrum disorder [38], and a cluster of nervous system problems including memory loss and finger tremors [39]. The same review also reported that occupational exposure studies of adult forestry workers did not report adverse effects, suggesting that early life development is a period of heightened vulnerability at levels lower than those triggering poisoning in healthy adults [40].

Biomonitoring by the Centers for Disease Control and Prevention (CDC) finds that chronic neonic exposure is widespread in the U.S. population [41], with more recent testing of 171 pregnant women from across the country and Puerto Rico finding neonics in the bodies of over 95% of participants, with levels rising over the course of the four-year study (2017–2020) [42]. Because the human brain has only a very limited ability to repair or recover from neurotoxic assault, even transient or low levels of exposure to environmental pollutants such as lead, mercury, air pollution and neurotoxic pesticides like chlorpyrifos can have lasting adverse effects [43, 44]. A study we recently published reviews the evidence of developmental neurotoxicity associated with neonics. We report on rodent laboratory toxicology studies sponsored by the manufacturer (the 'registrant') exposed to neonics during prenatal and early postnatal development that resulted in statistically significant shrinkage of brain tissue in high-dose offspring for five neonicotinoids: acetamiprid, clothianidin, imidacloprid, thiacloprid, and thiamethoxam [45].

Given that workers are largely people of reproductive age, and may also include individuals that are pregnant or breastfeeding, occupational exposures to neonics may pose a risk not only for the exposed adult, but also for the next generation. EPA found that most occupational risks for imidacloprid could only meet the regulatory approval standard if workers wear a long-sleeved shirt, long pants, shoes and socks, or with personal protective equipment (PPE) and gloves, and in some cases would need to wear double layer clothing and gloves [46]. For clothianidin and thiamethoxam, EPA's PPE requirements are similar except that some occupational tasks also require use of a respirator [47].

Fundamentally, PPE is an attempt to provide a barrier between the person and the hazard, but the hazard remains. For this reason, PPE should only be used as a last line of defense [48–52]. The workplace Hierarchy of Controls describes the most effective approach being elimination of the hazard, followed by reducing it through substitution, with PPE being the least effective safeguard measure [53]. Similarly, the essential-use approach, in a regulatory setting, aims to reduce hazardous chemicals by eliminating all nonessential uses, based on the foundational value that we should not use chemicals of concern in products or processes where they are not critical for health, safety, or the function of society [54, 55]. For neonics, the most effective prevention strategy – elimination—can be readily employed since the vast majority of neonic uses are applied in the absence of an actual pest problem, and are thus non-essential [56, 57].

While most of the reported acute poisoning incidents discussed in this paper are non-occupational incidents and non-agricultural uses of the pesticides, three neonics—imidacloprid, clothianidin and thiamethoxam—are also approved for over 100 different products used to coat or "treat" crop seeds. Pesticide seed treatments take advantage of the systemic nature of the chemicals. The coatings are designed to be absorbed through a plant's roots as it grows, making all of the plant's tissues including the pollen and nectar poisonous to target pests and beneficial insects such as bees, butterflies, and other pollinators [58–60]. Though the use of seed treatments is not tracked, one can estimate it by examining U.S. Geological Survey (USGS) Pesticide Use annual reports, which beginning in 2015 discontinued reporting on the seed treatment applications [61]. The precipitous drop in reported use from 2014 to 2015 can be presumed to be roughly the amount used as seed treatments that are no longer reported. USGS reports indicate that agricultural uses of thiamethoxam are almost all from seed treatments (1.2 million pounds per year, lbs/year, on corn and soy seeds, and about 0.2 million lbs/year for non-seed uses), and the case is similar for clothianidin (3.5 million lbs/year on corn seed treatments, and about 0.1 million lbs/year for non-seed uses). Imidacloprid agricultural use is split about half and half (with about 1 million lbs/year for soybean and cotton seed treatments, and about 1 million lbs/year on non-seed uses).

In 2024, EPA updated its occupational risks for neonics to include health risks to workers treating seeds with pesticides and handling treated seeds; EPA identified several activities that posed elevated risks to workers, including cleaning seed treatment equipment, even when maximum personal protective equipment (PPE) is used (double-layered clothing and a respirator rated with a protection factor of 10, PF-10) [62]. Of concern, PPE is often uncomfortable, poorly fitted, difficult to wear while doing work tasks, and can be less effective in higher temperatures such as during outdoor farmwork [63, 64]. A small study that conducted biomonitoring (urine samples) and tap water testing of Iowa farm families found that for people that worked directly with pesticides including treated seeds, occupational exposures and house dust was their greatest source of exposure [65].

While regulatory agencies require PPE to be used in occupational settings, that is often impractical or impossible for many of the consumer uses that led to the acute human poisonings reported in this paper. Applying pesticides on lawns, gardens, around homes, and on pets can cause poisonings in people that come into contact with the treated surfaces hours or even days after the initial product application. For example, the Seresto® flea and tick collars for pets include a warning on the package against letting children play with the collar, but children are frequently in close extended direct contact with their pets. The collar is made with a mix of imidacloprid and a non-neonic pesticide called flumethrin, which is "released from the collar" over time, according to the product website [66]. Pesticide residues on lawns, parks, and playground equipment can all be a source of non-occupational exposure to people without PPE.

In its 2020 imidacloprid evaluation and proposed regulatory determination – part of a federally mandated periodic review process known as "registration review" – EPA noted that, "[t]he total number of imidacloprid incidents reported to IDS, from 2013 to 2018, appeared to be increasing over time. The agency will continue to monitor the incident data and if a concern is triggered, additional analysis will be conducted [46]". The U.S. Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) and the Federal Food Drug and Cosmetic Act (FFDCA) require EPA to cancel a pesticide registration when existing risks related to its use are unacceptable and registrants have not made changes to the registration to address the unacceptable risks [67]. EPA is underestimating or ignoring neurodevelopmental and endocrine risks of neonicotinoid pesticides, which we have asserted is a violation of federal law. Even so, EPA's proposed 2020 regulatory determination for imidacloprid still found that cancellation of residential imidacloprid lawn sprays was "necessary" under federal law to "eliminate risks of concern to both children and adults from the residential turf use [46]". However, due to significant delays in the regulatory process, the proposed determinations were never finalized, and new "amended" proposed determinations are expected to be issued in 2025 [68].

Other jurisdictions have imposed significant restrictions on neonicotinoid uses, often for environmental reasons. Between 2013 and 2018, the European Union (EU) prohibited nearly all outdoor uses of the three most-used neonicotinoid active ingredients [69] – clothianidin, imidacloprid, and thiamethoxam – but EU-based agrochemical companies continue to produce and export them, largely to low- and middle-income countries [70]. In Canada, the federal government has imposed a number of restrictions on neonicotinoid use to protect pollinators and aquatic ecosystems in the last several years [71], with the provincial governments of Ontario and Québec requiring the identification and certification of a legitimate pest-control need before using neonicotinoid seed treatments for major field crops [72]. The result, at least in Québec, has been a near elimination of neonicotinoid seed coatings for these crops [73].

In absence of action by the federal government, a number of U.S. states have also enacted restrictions on neonicotinoid use. New York and Vermont recently became

the first two states to restrict the use of neonicotinoids on crop seeds, adopting the "verification of need" model pioneered in Ontario and Québec [74]. New Jersey [75], New York [74], Nevada [76], and Maine [36] have also banned most neonicotinoid use on lawns, gardens, and other non-agricultural landscapes, while Minnesota has prohibited neonicotinoid use on state lands [77]. Eleven states have also restricted most or all outdoor neonicotinoid use to certified applicators – which has the effect of removing neonicotinoid lawn and garden products from retail store shelves, but still allows for agricultural use, indoor use, and applications provided by most commercial lawn care or pest control providers [78].

Conclusion

Here we have presented an analysis of non-occupational human poisoning incidents associated with neonicotinoid pesticides, as reported in EPA's Incident Database System. While the data have recently become available to the public, they are not in a form that can be aggregated for analysis. Here we have done the work of aggregating and then individually evaluating each of the data summary reports (EPA does not make the full reports publicly available). This information is particularly important as local, state, and federal agencies grapple with how to address the impacts to workers, families, communities and ecosystems from the widespread use of this class of neurotoxic and developmentally neurotoxic insecticides. We reviewed 842 non-occupational human poisoning incidents associated with neonics in the IDS from 2018 through 2022. There are four human fatality reports, two associated with clothianidin and two with acetamiprid. People reported headaches, dizziness, nausea and skin irritation from using lawn and garden insect repellents, home pest treatments for bed bugs or roaches, and pet products made with imidacloprid or dinotefuran. In addition to the acute poisoning incidents reported in this paper, there is also evidence from rodent toxicology and human epidemiology linking early-life exposure to neonics with lasting neurodevelopmental harm [45]. And, neonics are regularly detected in waterways including drinking water sources, fresh fruits and vegetables, and human body fluids including breast milk and cerebrospinal fluid.

Regulatory agencies worldwide should use their legal authority to cancel unsafe products and unnecessary uses – including from seed treatments, and residential pet and lawncare products—to prevent further human poisoning, environmental contamination, and wildlife harm. Such actions would be consistent with One Health approach advanced by the World Health Organization (WHO), the World Organization for Animal Health (WOAH), the United Nations Food and Agriculture Organization (FAO) and the United Nations Environment Programme (UNEP). It's goal is to optimize the health of people, animals and the environment by ensuring food and water safety, reducing environmental contamination, and protecting biodiversity including pollinators and other beneficial insects [79].

Abbreviations

CDC	Centers for Disease Control and Prevention
COPD	Chronic obstructive pulmonary disease
EMS	Emergency medical services
EPA	U.S. Environmental Protection Agency
EU	European Union
FAO	United Nations Food and Agriculture Organization
FFDCA	Federal Food Drug and Cosmetic Act
FIFRA	U.S. Federal Insecticide, Fungicide and Rodenticide Act
FOIA	U.S. Freedom of Information Act
FQPA	U.S. Food Quality Protection Act
HazMat	Hazardous Materials
H-A	Human fatality
H-B	Human major injuries
H-C	Human moderate injuries
H–D	Human minor injuries
IDS	EPA Incident Data System
nAChR	Nicotinic acetylcholine receptor
Neonics	Neonicotinoid pesticides
NIOSH	U.S. National Institute for Occupational Safety and Health
NPIC	National Pesticide Information Center
PF-10	Respirator with a protection factor of 10
PISP	California Pesticide Illness Surveillance Program
PPE	Personal Protective Equipment
SDS	Safety Data Sheet
SENSOR	Sentinel Event Notification System for Occupational Risk
UNEP	United Nations Environment Programme
USGS	U.S. Geological Survey
WHO	World Health Organization
WOAH	World Organization for Animal Health

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

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Authors' contributions

J.B.S. conducted all the data analysis and wrote the main manuscript text. D.R. contributed portions of the manuscript including policy and legal analysis. All authors reviewed the manuscript.

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Data availability

The poisoning reports are now publicly available on EPA's online Incident Data System database. https://www.epa.gov/pesticide-incidents/about-incident-data-system-ids.

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Neonicotinoid pesticides: evidence of developmental neurotoxicity from regulatory rodent studies

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Neonicotinoids are the most widely used class of insecticides in the United States (U.S.). and the world. Consistent with their high use and persistence, neonicotinoids are often found contaminating drinking water and food. They are also detected in human urine, breast milk, amniotic and cerebrospinal fluids, as well as the brains of treated rodents. Neonicotinoids were once thought to pose little neurotoxic risk to humans, but a growing body of research challenges that assumption. In this study we provide the first comprehensive assessment of unpublished rodent developmental neurotoxicity (DNT) studies on five neonicotinoids that were submitted to the U.S. Environmental Protection Agency (EPA) by neonicotinoid manufacturers. Groups of female rats were administered three different doses of a neonicotinoid during pregnancy and lactation, and their offspring subjected to various neurological tests and brain measurements. We identified nicotine-like effects such as reduced brain size, indicative of neuronal cell loss. Statistically significant shrinkage of brain tissue was observed in high-dose offspring for five neonicotinoids: acetamiprid, clothianidin, imidacloprid, thiacloprid, and thiamethoxam. Two brain regions reduced in the rodent studies–the corpus callosum and caudate-putamen–tend to be smaller in people diagnosed with attention-deficit hyperactivity disorder (ADHD), and in children of mothers who smoked during pregnancy, suggesting a possible link between perinatal neonicotinoid exposure and ADHD. A decreased auditory startle reflex was reported for acetamiprid at all doses and was statistically significant in the mid- and high-dose offspring, and for clothianidin in juvenile high-dose females. No mid- or low-dose brain morphometric data were submitted for acetamiprid, imidacloprid, or thiacloprid. Thiamethoxam mid- and low-dose brain morphometric data were provided to EPA upon request. Only partial mid-dose brain morphometry data were submitted for clothianidin, but no low-dose data. Yet despite this lack of data, EPA concluded that only the high-dose brain morphometric effects were treatment-related–setting the mid-dose as the study's No Observed Adverse Effect Level (NOAEL) or failing to find a definitive NOAEL for acetamiprid, clothianidin, imidacloprid, thiacloprid and thiamethoxam. We found numerous deficiencies in EPA's regulatory oversight and data analyses. EPA dismissed statistically significant adverse effects, accepted substandard DNT studies despite lack of valid positive control data, and allowed neonicotinoid registrants to unduly influence agency decision-making. We conclude that perinatal exposure to neonicotinoids and their metabolites induces adverse, nicotine-like neurotoxic effects in rodent bioassays, and that the exposure limits set by EPA for human exposure are either not protective or not

supported by available neurotoxicity data. We propose regulatory changes to empower EPA to better protect public health from developmental neurotoxins like neonicotinoids.

KEYWORDS

pesticide, neurotoxic, DNT, neonicotinoid, EPA-environmental protection agency, neurodevelopment, developmental, brain

Introduction

Most major classes of insecticides act by disrupting the nervous system through pathways that are conserved across invertebrate and vertebrate species (U.S. EPA, 2024b). For instance, both the organophosphate (OP) and the carbamate classes of insecticides are designed to disrupt cholinergic nerve function (Soltaninejad and Shadnia, 2014). Similarly, a newer class of insecticides, the neonicotinoids (neonics), act as cholinergic receptor agonists by binding to nicotinic acetylcholine receptors (nAChRs), which results in the opening of calcium and other cation channels. By this mechanism the neonicotinoid pesticides exert their lethal effect on invertebrates (Tomizawa and Casida, 2003).

Neonics are now the most widely used insecticides in the US and globally with over three-quarters of neonicotinoids used as seed treatments, coated onto seeds of crops before dispersal (see Figure 1) (Douglas and Tooker, 2015; Douglas et al., 2024). Neonicotinoid seed coatings have dramatically expanded the amount of farmland treated with insecticides: at least 150 million acres in 2012 (Steeger, 2014), six times the amount of land treated with the top ten insecticides combined in 2001 (U.S. EPA, 2024b). Non-agricultural uses of neonics include lawns and gardens, parks and playgrounds, indoor bed bug treatment, and flea and tick treatments for pets.

With such widespread use, neonics routinely contaminate: waterways and tap water (Goulson, 2013; Klarich Wong et al., 2019; Millemann et al., 2020; Aggarwal, 2021); foods including fruits, vegetables and baby foods (Craddock et al., 2019; Zhang et al., 2019; USDA, 2022); and even human breast milk (Chen et al., 2020). Based on these food and water monitoring reports, it seems likely that a child growing up today may have been exposed to neonic pesticides during fetal development from *in utero* exposure, in infancy from contaminated breast milk and formula reconstituted with neonic-contaminated tap water, and into childhood from consuming contaminated drinking water and baby foods. Programs that conduct pesticide food and water monitoring, as well as biomonitoring, should continue and be expanded.

Given the potential for people to be regularly exposed to neonicotinoids, including during vulnerable periods of early life development, it is important to ensure that risk evaluations and regulatory approval of these neurotoxic insecticides meet (and hopefully exceed) the legal protections required by federal pesticide law.

The rodent Developmental Neurotoxicity Study (DNT) is one of several studies EPA uses to determine whether a pesticide poses a particular risk when exposures take place during early development of the brain and nervous system. This is because fetal and early infant life is when the mammalian brain and nervous system is being built. Neurotransmitters and their receptors help coordinate the process; they promote cell replication, initiate differentiation into different cell types, trigger then terminate formation of axons and synapses, regulate cell death and promote cell migration to specific brain regions to form the final architecture of the brain (England et al., 2017; Loser et al., 2021). If this complex and fragile developmental process is disrupted by xenobiotics, there is little opportunity for repair, and the damage can be permanent (Rice and Barone, 2000). The DNT study is known as a "guideline" study because it follows standardized Test Guidelines (U.S. EPA, 1998; OECD, 2007) to provide regulatory agencies with information needed to determine dose-response values and exposure limits.

Generally speaking, EPA sets maximum limits for acute (one-time) and chronic (lifetime) exposure by first deriving a no observed adverse effect level (NOAEL) from one or more guideline animal studies conducted with a pesticide. To set the human exposure limit, EPA divides the NOAEL by an uncertainty factor that is normally 100 (10 for interspecies extrapolation from a rodent study, and 10 for intraspecies differences across the human population) (U.S. EPA, 2002c). However, neither factor accounts for the greater susceptibility to pesticidal harm when exposure occurs *in utero* or in early life.

The Food Quality Protection Act (FQPA) of 1996 mandated that EPA consider available information concerning "the special susceptibility of infants and children," including "neurological differences between infants and children and adults, and effects of *in utero* exposure to pesticide chemicals," to ensure a "reasonable certainty" that "no harm" will result "from aggregate exposure" to a pesticide, including "all anticipated dietary and all other exposures for which there is reliable information" (FQPA, 1996).

The FQPA child protective factor is one way EPA can ensure a margin of protection–by reducing allowable exposure by a factor of 10 to account for the greater susceptibility of the young to developmental toxicants (EPA, 2002a). FQPA puts the burden of proof squarely on EPA to ensure that all uses of a pesticide meet the "reasonable certainty of no harm" standard for the general population and for every age group of children, including aggregate exposures from food, drinking water, and all household uses such as flea treatments for pets. The FQPA also mandates cumulative assessment of pesticides that share a common mechanism of toxicity. By law, EPA can modify or eliminate the FQPA 10X safety factor "only if, on the basis of reliable data, such margin will be safe for infants and children." (FQPA, 1996). Unfortunately, EPA has too often reduced or removed this important child-protection factor from its pesticide assessments, including for the neonicotinoids (Naidenko, 2020).

Evaluation of registrant developmental neurotoxicity studies

As part of implementing the FQPA, the EPA has required pesticide manufacturers (called "registrants") to conduct a rodent

TABLE 1 Summary of significant adverse findings identified by EPA Data Evaluation Records (DERs) of Registrant-sponsored Developmental Neurotoxicity (DNT) studies for neonicotinoid pesticides.

		Acetamiprid	Clothianidin	Imidacloprid	Thiacloprid	Thiamethoxam
Brain tissue thinning	High dose	Yes	Yes	Yes	Yes	Yes
	Mid dose	No data	Partial data	No data	No data	Yes
	Low dose	No data	No data	No data	No data	Yes
Decreased auditory startle reflex	High dose	Yes	Yes			
	Mid dose	Yes	Yes			
	Low dose	Yes				
Decreased motor activity	High dose		Yes	Yes		
	Mid dose			Yes		
	Low dose					
Learning and behavior effects	High dose				Yes	
	Mid dose				Yes	
	Low dose					
Delayed sexual maturation	High dose				Yes	Yes
	Mid dose				Yes	Yes
	Low dose					Yes

test following a guideline specifically for DNT (U.S. EPA, 1998; OECD, 2007). The guideline method specifies that groups of female rats are fed differing doses of the test substance during pregnancy and lactation to assess potential effects on the neurological development through adulthood (postnatal day 60 or later) of offspring exposed *in utero* and in mother's milk. The DNT guideline test includes neuropathology assessments, neurobehavioral endpoints, and body weight and other parameters common to other toxicity studies. There are four test methods for behavior: a functional observation battery (FOB); an open-field locomotor test to measure motor activity; an auditory startle test that measures the reflexive response to intense acoustic stimuli; and some tests for learning and memory such as a water maze test and a passive avoidance test. Developmental landmarks are recorded, including the ability to roll and reflexes for surface righting, time of eye opening and pupil constriction reflexes, and vaginal patency in females and preputial separation in males. Post-mortem observations include brain weight and brain histology to evaluate potential neuropathology. At postnatal day (PND) 11 and study termination, morphometric analysis to assess structural development of the brain is performed on various brain regions, such as structures within the neocortex, hippocampus and cerebellum, as well as subcortical regions like caudate-putamen and corpus callosum (U.S. EPA, 1998). The DNT study can be used to establish an acceptable exposure threshold for an acute (single) exposure, known as the acute reference dose, because "there is a presumption that effects during development may result from a single exposure" (U.S. EPA, 2002c).

Here we evaluate EPA's DNT Data Evaluation Records (DERs), comprehensive evaluations prepared by EPA staff, for five unpublished DNT studies submitted to EPA by neonicotinoid manufacturers.

Although EPA produced a summary data report for dinotefuran, we did not include it in our analysis because it did not record any significant adverse effects. EPA noted that there were no adverse effects on litter number or offspring viability at the high dose, and that there were no deficiencies with the study; it was classified by EPA as "acceptable" (U.S. EPA, 2013).

Below and summarized in Table 1, we report evidence of brain tissue thinning in at least some of the offspring in the high dose treatment group of DNT studies with all five of the neonics we analyzed–acetamiprid, clothianidin, imidacloprid, thiacloprid, and thiamethoxam. The DNT guideline only requires that brain morphometric data be submitted to EPA for the mid and low dose groups if there is pathology in the high dose group. Unfortunately, other than for thiamethoxam, EPA received either no data or only partial data from each registrant for the mid and low dose groups. Even lacking brain morphometric data for mid and low doses, EPA presumed that the effect was only at the high dose. Other endpoints where EPA reported statistically significant adverse effects are discussed, and identified in the Table as "yes." Where no statistically significant effects were identified, the space is left blank in the Table.

Acetamiprid

In a 2003 DNT study sponsored by Nippon Soda (Nemec, 2003), acetamiprid was administered via gavage to pregnant/lactating rats at doses of 0, 2.5, 10 or 45 mg/kg/day from gestation day 6 (GD6) through PND21. The study was first assessed in 2004, then revisited in 2007 and 2008 in response to the sponsor's objections (U.S. EPA, 2008). EPA reviewers were unable to conclude whether or not acetamiprid affected learning or memory due to high variability

TABLE 2 Summary of acute dietary exposure and risk estimates for acetamiprid.

Population subgroup	Acute Exposure (mg/kg/day) at the 95th Percentile*	% of Maximum "Safe" Exposure (aPAD) (mg/kg/day)	
		EPA aPAD = 0.1	Protective aPAD = 0.0025
All infants (<1 year)	0.069137	69%	2765%
Children 1–2 years	0.086734	87%	3469%
Children 3–5 years	0.064385	64%	2575%

[a]For acute exposure levels, see EPA. (2017), Table 5.4.5.1, p. 29.

in the test results, and effects on motor activity were uncertain due to problems with the control data: namely, that the normal developmental pattern for locomotion and motor activity was not seen in male control animals, and that the level of motor activity in control males seemed high. Brain morphometric data were only provided for the control and high dose animals. At PND72, the length of the ventral limb of the dentate hilus of the hippocampal formation was reduced by 15% in both male and female offspring, a statistically significant finding in the females (U.S. EPA, 2008).

The agency identified a dose-responsive decrease in the maximum auditory startle response in male offspring of all dosage groups at both timepoints (PND20/PND60): low-dose 15%/10%; mid-dose 27%/40%; and high-dose 42%/53% (U.S. EPA, 2008). The EPA's statistical analysis identified the mid-dose as a significant effect level when data from male and female pups from PND20 and 60 were combined. The registrant contested EPA's conclusions in a rebuttal report, arguing that the mid-dose was a no-effect level based on statistical analyses by two consulting groups (U.S. EPA, 2008). EPA statisticians rejected the consultants' analyses due to inappropriate use of models and statistical errors (U.S. EPA, 2008). The European Food Safety Authority (EFSA et al., 2024) likewise rejected the pesticide industry's statistical interpretation and set a no-effect level at the low dose of 2.5 mg/kg/day (EFSA, 2015). With the standard 100X uncertainty factor and the 10X FQPA child protective factor, the maximum acute exposure level regarded as safe for infants and children, known as the acute population, adjusted dose (aPAD), would be 2.5/1,000 = 0.0025 mg/kg/day.

In 2008, the EPA without explanation overruled its own statisticians' conclusions and raised the offspring NOAEL to the mid-dose of 10 mg/kg/day in accordance with the registrant's request (U.S. EPA, 2008). In 2017, EPA removed the FQPA child protective factor (reduced from 10X to 1X) in part based on the DNT study (U.S. EPA, 2017). These two changes together increased the aPAD by 40-fold to 0.1 mg/kg/day.

In Table 2, we show how these different aPADs result in radically different risk pictures (see Table 2 footnote). Based on EPA's upperbound estimates of acute dietary exposure to acetamiprid, infants and children are exposed to 64%–87% of EPA's official aPAD–where anything under 100% is considered acceptable (U.S. EPA, 2017). In contrast, that same exposure level exceeds a protective aPAD of 0.0025 mg/kg/day by a substantial 25–35-fold. Details on how EPA calculates dietary risk is in the 2017 acetamiprid draft human health risk assessment (U.S. EPA, 2017). In brief, dietary exposure is calculated as the combined exposure from both food residues and drinking water sources. Drinking water levels are predicted for both surface and groundwater sources using models. Food exposure is predicted using models populated with food consumption data from the US Department of Agriculture's survey of "What We Eat in America." Age-adjusted body weights and ingestion factors come from EPA's Exposure Factors Handbook (U.S. EPA, 2024a).

The more protective aPAD we propose for acetamiprid, 0.0025 mg/kg/day, is similar to what the European Food Safety Authority (EFSA) is now proposing. EFSA is recommending that the acceptable daily intake (ADI) of acetamiprid be lowered from 0.025 down to 0.005 mg/kg per day, to be more protective of potential developmental neurotoxicity risks (EFSA et al., 2024). EFSA's 84-page report supporting the recommendation includes the results of a systematic review of public literature discussing evidence of acetamiprid and DNT effects from both *in vitro* and *in vivo* studies, including ones cited in this manuscript. We refer readers to that report for further details.

Clothianidin

In a DNT study sponsored by Takeda Chemical Industries in 2000, female rats were fed clothianidin in the diet from GD0 to PND22 at doses of 0, 13, 43 and 142 mg/kg/day during gestation (Hoberman, 2000).

EPA flagged several serious study deficiencies that, to our knowledge, were never remedied. The study sponsor failed to provide EPA with the brain morphometric data for the low dose group. At the mid-dose, morphometric data were provided for females but not for males. For the mid dose females the brain morphometry data was provided to EPA only as a mean of both brain hemispheres, instead of separately (U.S. EPA, 2005). EPA noted all this in its list of study deficiencies and requested that any additional morphometric measurements should be submitted to EPA. Additional study deficiencies noted by EPA included no mention of any test results for pupillary function such as constriction and response to light.

Of the 17 brain measurements taken at PND12 and termination, among the high dose animals, statistically significant differences were reported for 6 measurements in females (2 increased, and 4 decreased) and 3 measurements in males (two increased, and 1 decreased). At termination, the 4 reported differences were all decreases (3 in females, 1 in males), suggesting that by about 3 months of age (PND83-87) the neurodevelopmental effects of clothianidin may include a thinning of brain tissues.

For the mid dose brain morphometric data for females, there were no statistically significant effects on brain measurements (U.S. EPA, 2005). It remains unknown whether the conclusion may have been different had the registrant submitted data for the individual hemispheres, and if the male data had also been submitted. The study remains classified as deficient for lacking this information.

Despite this, EPA set the offspring neurotoxicity NOAEL at the mid-dose based on high-dose effects, including decreased motor activity (number and duration of movements) in male offspring, decreased auditory startle response in female offspring and, at termination (PND83-87), a 5% thinning of the hippocampal gyrus in both sexes and a 6% reduction in caudate putamen thickness in females (U.S. EPA, 2005).

Imidacloprid

In a 2001 DNT study conducted by Bayer (Sheets, 2001), imidacloprid was fed to three groups of pregnant/lactating Wistar rats from GD0 to PND21. Doses during gestation were 0, 8, 19 and 55 mg/kg/day. After weaning, offspring were given untreated feed and evaluated until 75 days of age.

EPA identified two major treatment-related neurodevelopmental effects (U.S. EPA, 2002b). First, the thickness of the caudate/putamen brain region was reduced by 5.4% in high-dose female pups at PND11 and by 2% at study termination (PND70), described by EPA as a "persistent change" in this structure. Second, motor activity was reduced in high-dose male and female pups at PND17, and in female pups at PND21 (U.S. EPA, 2002b). Though not statistically significant, EPA regarded the reduced motor activity as treatment-related and adverse due to its consistency in both sexes and magnitude (31%–38%). In a separate review of the same study, the California Department of Pesticide Regulation found a significant 27% reduction in the thickness of the corpus callosum in high-dose females at PND11 (Cal, 2006). The corpus callosum effects were not identified or reported by EPA.

Bayer did not comply with an EPA directive to supply caudate/putamen morphometric measurements for low- or mid-dose female animals (U.S. EPA 2002b), as required by both EPA and OECD Test Guidelines (U.S. EPA, 1998, OECD, 2007). Despite not having adequate data to assess harmful effects on the caudate/putamen, corpus callosum or other brain structures at the low- and mid-dose, in 2002 EPA set the offspring NOAEL at the mid-dose (U.S. EPA, 2002b).

Thiacloprid

In a 2001 DNT study sponsored by Bayer Corporation (Hoberman, 2001), female rats were administered thiacloprid in the diet from GD0 to PND22 at 0, 4.4, 25.6 and 40.8 mg/kg/day during gestation. Brain weight and neuropathology were assessed at PND12 and PND68-79. A number of brain regions were adversely affected in male offspring at the high dose, including statistically significant 4% reductions in the corpus striatum, a region that encompasses the caudate-putamen, at both PND12 and termination; a 14% reduction in the corpus callosum at PND12; and a 5% reduction in the dentate gyrus at termination. EPA noted that "a definitive NOAEL was not established for these findings" given the lack of data for the mid- and low-doses (U.S. EPA, 2003a).

In tests of passive avoidance and behavior retention, females showed significantly poorer performance at the mid-dose and high-dose treatments compared with controls (U.S. EPA, 2003a). EPA identified "suggestive effects" on motor activity and auditory startle reflex in both the mid- and high-dose groups that were not statistically significant.

Sexual maturation was statistically significantly delayed by an average of a half to a full day in the mid and high dose male pups (as measured by preputial separation), and in the high dose female pups (as measured by vaginal patency) (U.S. EPA, 2003a). These are measurements of hormone-dependent developmental landmarks of sexual maturity that occur at the time of puberty in both rats and humans.

EPA's documented concerns with the positive control data that was submitted with the study were substantial: "Most of the positive control studies are unacceptable for use with the current study. . . . None of the studies demonstrated the laboratory's ability to detect major functional neurotoxic endpoints using the observational methods used in the current study." (U.S. EPA, 2003a). EPA's list of study deficiencies was a page long, with the lack of acceptable positive control data listed last. Other study deficiencies identified by EPA included: inadequate description of the methods used to evaluate functional behavior; motor activity never habituated, with no explanation provided; the termination of the study with final brain pathology data was over an 11-day period, with no explanation for this wide range of ages at study termination; brain measurements were made bilaterally but only reported as the mean value of both hemispheres; although treatment-related alterations in brain morphology were reported for the high-dose, the brain morphometry at the mid and low dose levels were required but were not received.

The study was judged "unacceptable" due to numerous serious deficiencies, including failure to supply brain morphometry, for low- and mid-dose groups. Because of this, EPA could not set a definitive NOAEL for offspring and arbitrarily applied a 3X "database uncertainty factor" in calculating the effect concentration (U.S. EPA, 2003b).

Thiamethoxam

In a 2003 DNT study sponsored by Syngenta Crop Protection Inc. (Brammer, 2003), thiamethoxam was administered in the diet to female rats from GD7 to PND22 at doses of 0, 4, 35 and 300 mg/kg/day during gestation. Brain morphometry was conducted on high-dose animals sacrificed at PND12 and at study termination on PND63. Upon request by EPA, Syngenta submitted mid- and low-dose brain morphometric data, which were analyzed in a separate DER in 2007 (U.S. EPA, 2007).

Thiamethoxam reduced brain weight significantly at termination in high-dose males and females as well as mid-dose females. Of the 14 brain regions/parameters that were analyzed in the male offspring at termination, 12 of the high-dose parameters were significantly reduced (by 5%–20%) compared with control animals (U.S. EPA, 2007). At the mid-dose, 9 of the parameters were reduced in size compared with controls, 6 of the regions were reduced by 2%–13%, and 3 were statistically significant reductions. Among low-dose male offspring at termination, 6 of 12 regions were reduced in size (by 5%–15%), and 2 were statistically significant (U.S. EPA, 2007).

The most consistently affected brain regions across sexes and doses were the dorsal cortex, the thalamus, and the corpus callosum–the latter's thickness reduced by 20% and 16% in high-dose males at termination and females at PND12, respectively (U.S. EPA, 2007). Significant changes in the male thalamus at termination included reduced height (high-dose), reduced width (mid- and high-dose), and decreased overall width of the thalamus/cortex (all doses). The thalamus width of females was significantly reduced in all dosage groups at PND12. The dorsal cortex thickness of males at termination was significantly reduced by 11%–15% in all dosage groups in one set of level 3 specimens, and by 6%–11% in high-dose males for three other sets of specimens (levels 3, 4 and 5).

Age at sexual maturation in male offspring (measured as preputial separation) was delayed across all thiamethoxam treatment groups, by an average of a half-day at the low dose and an average of 1.5 days at the high dose (U.S. EPA, 2007). The delay was statistically significant in the low ($p < 0.05$) and high dose group ($p < 0.01$), compared with control animals. EPA notes in its report that the study did not monitor or report on other developmental landmarks such as tooth eruption and ear pinna unfolding.

Despite the treatment-related effects in offspring of all dosage groups and both sexes, including reduced brain weight in mid-dose females, EPA concluded that only effects at the high dose were treatment-related and set the study offspring NOAEL at the mid-dose, 35 mg/kg/day (U.S. EPA, 2020).

Discussion

Our review of the EPA data reports for rodent DNT studies consistently found a significant reduction in brain tissue in high-dose offspring for five neonicotinoids: acetamiprid, clothianidin, imidacloprid, thiacloprid, and thiamethoxam.

Additionally, reported effects of acetamiprid include reduced auditory startle reflex at all doses, with statistical significance in the mid- and high-dose groups. The clothianidin DNT also reported reduced auditory startle reflex in high-dose juvenile females. Decreased motor activity was observed for clothianidin (high-dose males) and imidacloprid (high-dose in both sexes). The thiamethoxam DNT recorded delayed sexual maturation in male offspring across all doses that was statistically significant at the low and high dose. Thiacloprid was associated with poor behavior retention in mid- and high-dose females, and with delayed sexual maturation in the mid and high dose male pups, and in the high dose female pups (See Table 1).

Because the study sponsor failed to submit to EPA the required brain morphometric data for mid- or low-dose groups for acetamiprid, imidacloprid, or thiacloprid, a true NOAEL for the morphometric brain effects cannot be determined. Thiamethoxam's mid- and low-dose data were supplied to the EPA upon request. For clothianidin only the female mid-dose data were given to EPA, but not male mid-dose or the low dose for either sex. Despite these data gaps, EPA designated the mid dose (for which in most cases it had no data) as the NOAEL for all five neonic pesticides. In addition to the obvious problems with determining a NOAEL without supportive data, in some cases this determination was contrary to the recommendations of the scientist that reviewed the data (acetamiprid) or was made despite a lengthy list of concerns regarding study deficiencies (thiacloprid).

The precise mechanisms of the effects we identified are unclear, and it is beyond the scope of our study to explore them in detail (the regulatory DNT studies are intended only to identify endpoints associated with developmental neurotoxicity and to quantify potential differences in life-stage susceptibility, not investigate mode of action.) However, some insights might be gleaned from the extensive body of research on nicotine, a well-established developmental neurotoxin (Slotkin, 2008; England et al., 2017; Castro et al., 2023), based on their extensive similarities.

Nicotine-like effects of neonicotinoids on the cholinergic system in neurodevelopment

Neonicotinoids are similar in structure to nicotine, and like it are agonists of nicotinic acetylcholine receptors (nAChRs) (Kimura-Kuroda et al., 2012). Neonicotinoids penetrate the blood-brain barrier (Hirano et al., 2021; Katić et al., 2021) and access the fetal brain (Burke et al., 2018) in animal models. They are detected in human cerebrospinal fluid (Laubscher et al., 2022; Li et al., 2022), pass through the human placenta (Zhang et al., 2022), and are found in the breast milk of lactating women (Zhang et al., 2023). Fetal exposure to nicotine via maternal smoking has long been established (Luck et al., 1985).

The results of these DNT studies contribute to the growing evidence that neonicotinoids exert adverse, nicotine-like effects on the developing mammalian brain (Cal, 2006; Kimura-Kuroda et al., 2012). The reported dimensions of certain brain regions were nearly all smaller in adult offspring exposed perinatally to neonicotinoids, while overall brain weight declined in response to thiamethoxam. Reduced volume of the developing brain is a sensitive indicator of neuronal cell loss from exposure to developmental neurotoxicants (Kaufmann and Gröters, 2006). These findings are consistent with studies showing reduced neurogenesis and increased neuronal cell death in the hippocampus of neonatal mice exposed to either imidacloprid or acetamiprid (Nakayama et al., 2019), and decreased neurogenesis in mouse embryos following prenatal exposure to acetamiprid (Kagawa and Nagao, 2018).

Imaging studies have shown that fetal brain exposure to nicotine via maternal smoking during pregnancy also reduces human brain volume and the dimensions of certain brain regions (Anblagan et al., 2013; England et al., 2017), likewise via neuronal cell damage and death (Slotkin, 2008). And while maternal smoking involves perinatal exposure to many bioactive compounds in tobacco smoke that suppress overall fetal growth, animal models involving exposure to nicotine alone demonstrate nicotine-specific, cholinergic effects on fetal brain development at very early stages of development, even when subsequent birth weight is normal (England et al., 2017). Importantly, reduced brain dimensions in the rat DNT studies persisted in adult offspring (PND 63-87). Perinatal nicotine exposure likewise can cause changes in the trajectory of brain development that persist into maturity (Slotkin, 2008).

These similarities in the effects of neonicotinoids and nicotine on mammalian brain size beg the question of whether they may also trigger similar neurobehavioral outcomes.

As discussed above, the reduced brain dimensions in the DNT rat studies were accompanied by functional nervous system deficits:

decreased auditory startle reflex, decreased motor activity, and impaired learning, suggesting a possible link between brain effects and neurobehavioral outcomes. Interestingly, auditory processing defects are also effects of *in utero* nicotine exposure (Dwyer et al., 2008).

The brain structures most consistently reduced across rodent DNT studies were the corpus callosum and the caudate-putamen. The corpus callosum is a bundle of nerve fibers that connects the right and left hemispheres and processes sensory, motor and high-level cognitive signals (Goldstein et al., 2024). The caudate-putamen is part of the dorsal striatum, which is primarily involved in control over conscious motor movements and executive functions (Young et al., 2024). The neonicotinoid-induced reduction of these structures in rodent studies suggests a possible link to attention-deficit hyperactivity disorder (ADHD) in humans, for several reasons. First, imaging studies seeking neuroanatomical correlates of ADHD have found that people with clinically diagnosed ADHD tend to have smaller corpus callosa (Hynd et al., 1991; Giedd et al., 1994; Baumgardner et al., 1996; Semrud-Clikeman and Bledsoe, 2011; Yu et al., 2023), and in some studies reduced volume of the caudate-putamen as well (Valera et al., 2007; Emond et al., 2009). While these studies did not investigate potential causal factors, others have found a decrease in corpus callosum thickness in children born to mothers who smoked during pregnancy—suggesting a potential link with nicotine—in some cases accompanied by lack of coordination during information and auditory process (Bublitz and Stroud, 2012). Two additional studies find the corpus callosum reduction only in female (Paus et al., 2008) or male (Björnholm et al., 2020) children of maternal smokers. Finally, others have identified smoking during pregnancy as a risk factor for ADHD in their children, irrespective of possible anatomical anomalies of the brain (Milberger, et al., 1996; Milberger et al., 1998; Dong et al., 2018; Huang et al., 2018). That prenatal exposure to tobacco smoke (in humans) and neonicotinoids (in rats) both induce shrinkage of structures whose smaller size appears to be characteristic of ADHD, and that people having a mother who smoked during pregnancy is independently associated with ADHD, at least suggests the possibility that prenatal exposure to neonicotinoids in humans may increase risk of this disorder as well. While this hypothesis is largely correlational, it finds support in the common effects exerted by neonicotinoids and nicotine on mammalian brain development discussed above.

Of course, one must also consider exposure, and the fact that neonicotinoids show considerably less affinity for mammalian nAChRs than nicotine (Tomizawa and Casida, 2003). However, two neonicotinoids break down to form nicotinoid metabolites (desnitro-imidacloprid and descyano-thiacloprid) that have equal or greater potency as agonists of nAChRs in mammals relative to nicotine (Tomizawa and Casida, 2003). Imidacloprid is degraded to its desnitro form in the environment, in treated plants, and in the mammalian liver (Cal, 2006; Loser et al., 2021). Desnitro-imidacloprid is found in human urine (Wang et al., 2020) and in drinking water (Klarich et al., 2017). A preliminary risk assessment of dietary exposure to desnitro-imidacloprid in food concluded that internal levels could be high enough to activate nAChRs, and would even be more likely to desensitize these same receptors–with desensitization occurring at around 17 nM, roughly 10-fold lower than activating levels (Loser et al., 2021). This resembles the capacity of nicotine to desensitize rat nAChRs at the low, non-activating concentration of 10 nM (Paradiso and Steinbach, 2003). Neonicotinoid desensitization of nAChRs could be as problematic as activation, disrupting normal neuronal function and neurodevelopment (Loser et al., 2021) with potential effects on the operation of neural networks involved in memory and learning processes (Ochoa et al., 1989).

Because these metabolites of imidacloprid and thiacloprid have nicotine-like potency, one might expect to see neurodevelopmental impacts of exposure to their parent chemicals at low exposure levels. While we have not exhaustively reviewed the literature, two relevant studies conducted at doses near or below acute regulatory thresholds for human exposure stand out. Babeľová et al. (2017) orally exposed female mice to 0.03 mg/kg/day thiacloprid on days 1–3 of pregnancy, and found the isolated day 4 blastocytes exhibited significantly decreased cell numbers versus controls, cell loss that could ramify into neuronal cell deficits in the brain of developing fetuses. Saito et al. (2023) orally administered imidacloprid at 0.01 mg/kg/day or nicotine (0.1 mg/kg/day) to maternal mice from embryonic day 11 to 4 weeks after birth, and found that both imidacloprid and nicotine impaired certain aspects of learning and memory in male pups subjected to a water maze test.

Developmental neurotoxicity studies provide critical information, but must be conducted and overseen competently

Industry and EPA scientists who support *in vitro* approaches to assess DNT (discussed below) have argued that brain morphometry is unreliable because it is prone to "technical artifact" (Jackson et al., 2024). Yet when properly performed, morphometric analysis of brains can supply valuable data for regulators and is associated with less variability than body weight (Crofton, et al., 2001), a commonly used endpoint. The full suite of DNT test methods have been extensively validated; can provide reliable, relevant and reproducible data; and represent the best available science for assessing DNT potential in humans (Makris et al., 2009). However, improvements are needed. An analysis of 69 pesticide DNT study results submitted to EPA found that among the neurobehavioral tests, cognitive function and the FOB were used the least to determine a LOAEL, suggesting that within the guideline test they are not sufficiently sensitive endpoints (Vorhees and Makris, 2015). Locomotor activity and auditory startle were used most frequently for setting a LOAEL. Vorhees and Williams (2024) recommended updates to the DNT with additional requirements for more sensitive tests of learning and memory, while also noting that additional guidance may be helpful to improve the rigor of testing and reporting of results.

Deficiencies in DNT study data that do arise are often attributable to poor performance. An EPA review of positive control studies (studies undertaken with positive control chemicals known to disrupt neurological development) from labs that perform DNT studies found very troubling deficiencies; for instance, only three of the 16 demonstrated proficiency in testing for all DNT endpoints (Crofton et al., 2004). For 4 of the 5 DNT studies reviewed here (excepting clothianidin), adequate positive control data had either not been received or fully evaluated by EPA at the

time the DERs were written, potentially compromising the integrity and reliability of the test results. Indeed, for thiacloprid EPA noted that: "None of the [positive control] studies demonstrated the laboratory's ability to detect major functional neurotoxic endpoints using the observational methods used in the current study." (U.S. EPA, 2003a).

Poor scientific practices can also be perpetuated by deficient regulatory oversight. For instance, EPA flagged the failure to submit brain morphometry for mid- and/or low-dose animals as a study deficiency, but then went ahead and set a LOAEL at the high-dose and NOAEL at the mid-dose for acetamiprid, clothianidin, and imidacloprid with the presumption–in the absence of complete data–that there would be no adverse effects on the brain at the mid- and low-doses. We believe that such determinations should be based on data, not speculation. Other unremedied deficiencies identified by EPA included inadequate assessment of motor activity, learning and memory (acetamiprid), no reporting of criteria for scoring errors in the water maze tests (clothianidin and thiacloprid) and failure to report how functional observation assessments are conducted (clothianidin and thiacloprid). EPA thus accepts studies that it deems deficient and that may well miss important adverse neurological effects, and registrants face no consequences for failing to supply missing or inadequate data.

It is our opinion that the quality of rodent DNT and other regulatory toxicology studies would improve considerably if EPA were to reject seriously deficient studies, enforce requests for additional data, and cancel or refrain from approving or re-approving pesticides when reliable data are lacking.

Developmental neurotoxicity studies moving forward

There is considerable momentum at EPA's Office of Pesticide Programs to replace DNT rodent studies with new approach methodologies (NAMs) involving *in vitro* cell-based assays and *in silico* computational models (Crofton et al., 2014). The rationales most often cited are the time and expense of animal testing, and the laudable goal of reducing animal suffering (Crofton et al., 2014; Zaveri et al., 2019). However thus far, there is no adequate alternative to *in vivo* DNT studies (Vandenberg, and Zoeller, 2019). The OECD recently reviewed the DNT *in vitro* battery of tests (called the DNT IVB), warning that, "Several gaps in coverage of neurodevelopment processes and cell types have been acknowledged, including assays for neuroectodermal formation, peripheral nervous system specific processes, astrocyte differentiation and maturation, the blood-brain and placental barriers, microglia regulation of neuronal growth and connectivity, neuronal subtype specification, and axon myelination. . .. Also, the current DNT IVB does not fully account for sex or human genetic diversity that may influence susceptibility to chemical-induced developmental neurotoxicity (i.e., gene × environment interaction). These factors may result in lower sensitivity and specificity." (OECD, 2023).

The European Partnership for the Assessment of Risks from Chemicals (PARC), which includes authors from 22 government agencies and academic institutions, published an article in Frontiers in Toxicology in April 2024 concluding that the current DNT NAMs have too many gaps to be used in risk assessment at this time (Tal et al., 2024). PARC particularly identified functional gaps, including tests of cognitive and neurobehavioral outcomes, cell processes within whole organisms, and learning and memory. The PARC report notes that these gaps will remain even with the future-planned DNT NAMs tests, unless additional whole animal tests are included using zebrafish.

Instead of investing in updating the rodent DNT tests to improve the quality, rigor, and sensitivity to detect complex neurodevelopmental effects such as learning, memory and behavior, EPA has placed its confidence in the DNT NAMs tests. EPA is so confident in NAMs that it is relying on a lack of bioactivity in NAMs tests as evidence of lack of DNT, leading to less-protective risk estimates for several organophosphate pesticides (U.S. EPA, 2023; U.S. EPA, 2024c). This misuse of NAMs is strongly opposed by health scientists and regulators alike (Children's Health Protection Advisory Committee, 2021; Birnbaum, et al., 2024; Khan, 2024; Lam et al., 2024; Newell-Price, 2024).

Regulatory recommendations

EPA should make DNT studies a core requirement for registration of every pesticide, as its own scientists recommended in 1999 (U.S. EPA, 1999). This would reverse a disturbing trend of DNT study waivers that EPA has granted and even celebrated in recent years (Craig et al., 2019; Lerner, 2021).

Given the clear evidence of neonicotinoids' mammalian neurotoxicity, EPA should reduce the acute and chronic reference doses (exposure limits) for each of them by a factor of at least 10 to account for the special sensitivity of the developing nervous system, as mandated by the FQPA.

Because neonicotinoids and their metabolites share a common mechanism of toxicity with nicotine, EPA should conduct a cumulative assessment of these insecticides, as mandated by another provision of the FQPA. This could be accomplished by assigning each neonicotinoid and major metabolite a relative potency factor that accounts for the greater toxicity of certain metabolites.

The FQPA authorizes EPA to eliminate a 10X child protective factor only if it has reliable information to find reasonable certainty of no harm to children without that protection. Given the gaps in coverage and the lack of validation with DNT NAMs, the risks to human and environmental health, and scientific uncertainties are far too great for EPA to rely on negative results (no bioactivity results) from NAMs tests. Instead, EPA could follow a recommendation of its Children's Health Protection Advisory Committee, and employ NAMs results only to indicate or upgrade concern for a hazard, but not to conclude absence of hazard or to reduce the margin of protection afforded by the FQPA 10X child protective factor (CHPAC, 2021).

Conclusion

The rodent studies reviewed here provide valuable insights into the developmental neurotoxicity of five neonicotinoids, revealing similarities to the effects of nicotine, which is known

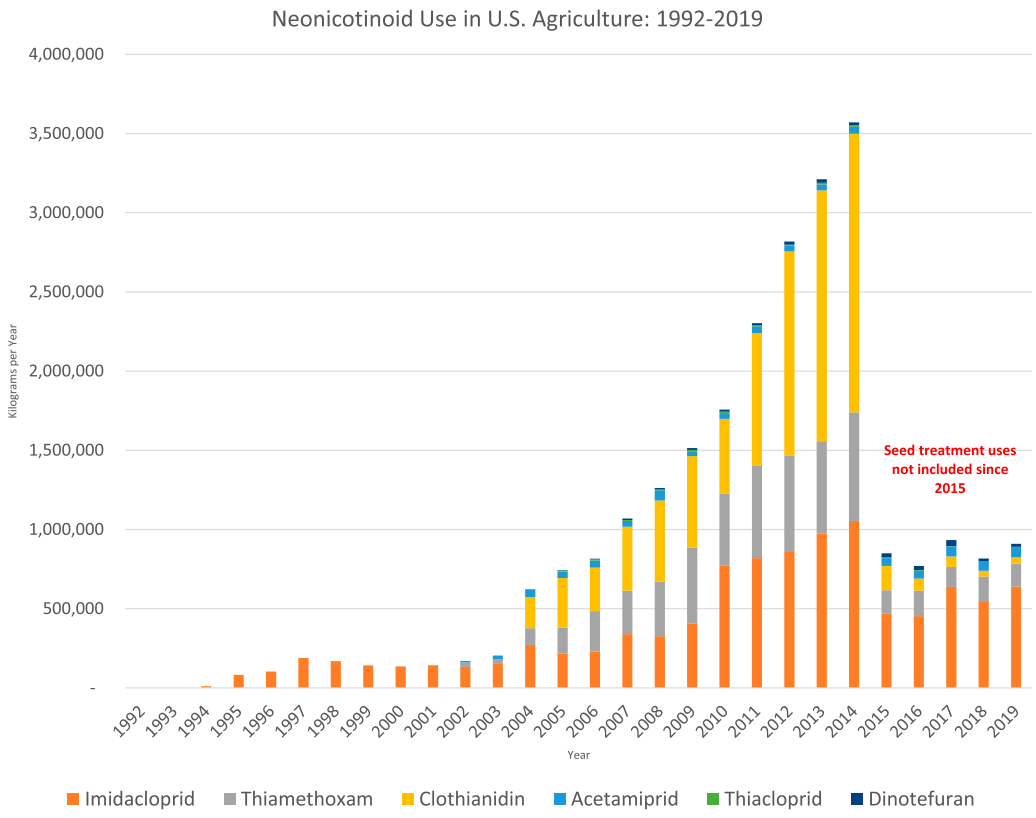

FIGURE 1
U.S. Geological survey data on neonicotinoid use (Wieben, 2021). Seed coating uses included up through 2014; Kynetec, the firm that supplies USGS with usage data, stopped reporting the amounts of neonicotinoids in seed coatings in 2015.

to disrupt mammalian neurological development. Early-life exposure to each neonicotinoid reduced the dimensions of various brain regions, signifying neuronal cell death and reduced neurogenesis. Shrinkage of the brain regions most consistently affected across studies–the corpus callosum and caudate-putamen–suggests a possible role in the genesis of attention-deficit hyperactivity disorder (ADHD). The studies also demonstrated reduced auditory startle response and suggested adverse effects on learning and memory.

Further research is needed into the developmental neurotoxicity of neonicotinoids, and in particular metabolites equipotent to nicotine, especially given the ubiquitous use of and exposure to these compounds and the potential for life-long impairment. The conduct and oversight of regulatory DNT studies on neonicotinoids and other pesticides must be improved so they can provide higher-quality data. Well-conducted rodent studies of sufficient statistical power and strict adherence to required animal welfare protections remain critical for assessing xenobiotic disruption of complex neurodevelopmental processes. While new approach methodologies (NAMs) may contribute valuable insights into the cellular and molecular mechanisms of such adverse effects, they are not currently capable of replacing *in vivo* assessments.

Summary

Neonicotinoid insecticides are widely used, environmentally persistent, and are detected in drinking water, foods, human urine, breast milk, amniotic and cerebrospinal fluids, and the brains of treated rodents. Here we provide the first comprehensive assessment of unpublished rodent developmental neurotoxicity (DNT) studies on five neonicotinoids sponsored by neonicotinoid manufacturers. Statistically significant shrinkage of brain tissue was observed in high-dose offspring for five neonicotinoids: acetamiprid, clothianidin, imidacloprid, thiacloprid, and thiamethoxam. A decreased auditory startle reflex was reported for acetamiprid at all doses and was statistically significant in the mid- and high-dose offspring, and for clothianidin in juvenile high-dose females.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

JS: Conceptualization, Formal Analysis, Investigation, Methodology, Validation, Visualization, Writing–original draft, Writing–review and editing. ND: Conceptualization, Formal Analysis, Investigation, Methodology, Validation, Writing–original draft, Writing–review and editing. WF: Conceptualization, Formal Analysis, Investigation, Methodology, Validation, Visualization, Writing–original draft, Writing–review and editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Los Angeles Times | ARTICLE COLLECTIONS

Pesticide blamed in death of 25,000 bumblebees in Oregon

June 21, 2013|By Devin Kelly | *This post has been corrected. See the note below for details.*

A pesticide used to control aphids has been singled out as the cause in this week's deaths of tens of thousands of bumblebees in a retail parking lot in Oregon, state officials said Friday.

At least 25,000 bees were found dead and more were dying in a Target parking lot in Wilsonville, about 18 miles southwest of Portland, in what experts have described as the largest known die-off of bees in the United States.

Witnesses reported bees falling from trees and littering the ground.

Crews worked Friday morning to wrap protective netting, purchased by the city, around the 55 European linden trees in the area. Workers stood on cherry-pickers to place the bee-proof shade material around the large trees, which are in full bloom.

On Monday, concerned calls from shoppers prompted the Xerces Society for Invertebrate Conservation -- a Portland-area conservation group -- to sound an alarm. The Oregon State Department of Agriculture responded by sending staff to collect samples of insects and foliage from the linden trees.

State officials were able to directly link the deaths to the pesticide Safari, which was sprayed on the trees Saturday to control aphids, the department said Friday in a statement. Officials have not yet identified the property management agency or the crews that applied the pesticide.

“It was a mistake to put it on linden trees in bloom,” said Dan Hilburn, director of plant programs with the Oregon State Department of Agriculture. Linden flowers contain nectar highly attractive to bees.

The pesticide, in a class called neonicotinoids, is lethal to bees and other pollinators. Honeybees, ladybird beetles (ladybugs) and syrphid flies were also found dead in the lot, said Scott Hoffman Black, executive director of the Xerces Society.

In terms of assessing penalties, investigators are focusing on whether the pesticide was applied inconsistently with its labeling, and whether the activity was conducted in a faulty, careless or negligent manner, said Dale Mitchell, the pesticide compliance program manager with the Oregon Department of Agriculture.

Violations can carry fines ranging from $1,000 to $10,000, Mitchell said.

In fact, the product label reads:

“This product is highly toxic to bees exposed to direct treatment or residues on blooming crops or weeds. Do not apply this product or allow it to drift to blooming crops or weeds if bees are visiting the treatment area.”

The environmental impact of neonicotinoids has come under increasing scrutiny worldwide. In April, the European Union banned the use of three types of neonicotinoid pesticides in crops that attract bees.

In the United States, one group, the Center for Food Safety, has sued the Environmental Protection Agency, saying that neonicotinoids are not regulated properly.

In a statement, the U.S. Environmental Protection Agency said it was aware of the Wilsonville bee deaths. “The EPA is tracking the incident closely but at this time we cannot comment on ongoing investigations,” the agency said.

The Wilsonville incident marked an ominous start to National Pollinator Week, an event designed to bring attention to the disappearance of bees. An estimated 10 million hives have been lost since colony collapse disorder first emerged in 2006.

Bumblebee hives are much smaller than honeybee hives, and an estimated 150 colonies were destroyed in Wilsonville, Black said.

[For the record, 5:22 p.m., June 25: An earlier version of this post said an estimated 10 billion hives been lost since colony collapse disorder first emerged in 2006. Only 10 million have been lost.**]**

More Than 25,000 Bees Die in Oregon

By Gillian Mohney
@gillianmohney

Jun 22, 2013 9:27pm

More than 25,000 bees were found dead in Wilsonville, Ore. (The Xerces Society for Invertebrate Conservatio/AP Photo)

The mystery of why thousands of bees fell from the sky has been solved, according to the Oregon Department of Agriculture.

The department announced Friday that it has determined an insecticide caused the deaths this week of 25,000 bees in Wilsonville, Ore.

The bees were found scattered across a parking lot earlier this week.

Mace Vaughn and his partner Rich Hatfield of the non-profit environmental group the Xerces Society worked with the Oregon Department of Agriculture to discover the cause by painstakingly picking up specimens of dead bees.

“We’ve lost a hundred, a hundred fifty colonies at least just from this area — just wiped them out,” Vaughn told ABCNews.com affiliate KATU-TV in Portland.

On Friday, the Oregon Department of Agriculture determined the bees were killed by an insecticide called Safari used to kill aphids. The trees where the insecticide was used are being netted to protect any surviving bees that might wander into the area.

The death of the bees in Oregon comes as colony collapse disorder threatens honey bee populations across the U.S.

According to the U.S. Department of Agriculture, beekeepers have been reported losing between 30 to 90 percent of their colonies since 2006. There is no known cause for the disorder, in which bees abruptly leave the hive.

AUGUST 19, 2013

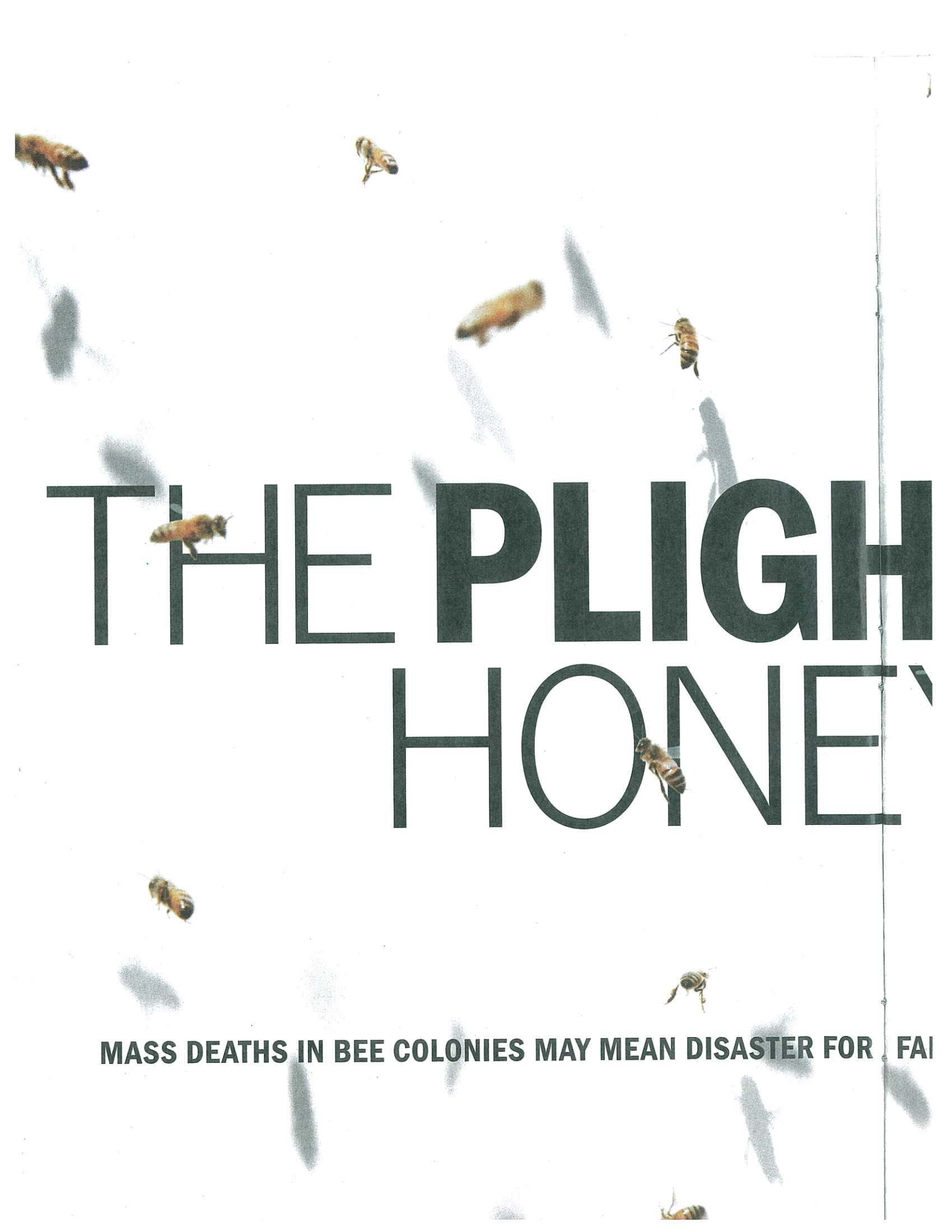
Zakaria: The new al-Qaeda threat / Ted Cruz / **Foroohar:** Yellen over Summers for Fed chief / Low Rolling in Vegas

TIME

A WORLD WITHOUT BEES

THE PRICE WE'LL PAY IF WE DON'T FIGURE OUT WHAT'S KILLING THE HONEYBEE

BY BRYAN WALSH



THE PLIGH
HONE

MASS DEATHS IN BEE COLONIES MAY MEAN DISASTER FOR FA

HT OF THE EYBEE

FOR FARMERS—AND YOUR FAVORITE FOODS BY BRYAN WALSH

Photomontage by Hannah Whitaker for TIME

YOU CAN THANK THE *APIS MELLIFERA*, better known as the Western honeybee, for 1 in every 3 mouthfuls of food you'll eat today. From the almond orchards of central California—where each spring billions of honeybees from across the U.S. arrive to pollinate a multibillion-dollar crop—to the blueberry bogs of Maine, the bees are the unsung, unpaid laborers of the American agricultural system, adding more than $15 billion in value to farming each year. In June, a Whole Foods store in Rhode Island, as part of a campaign to highlight the importance of honeybees, temporarily removed from its produce section all the food that depended on pollinators. Of 453 items, 237 vanished, including apples, lemons and zucchini and other squashes. Honeybees "are the glue that holds our agricultural system together," wrote journalist Hannah Nordhaus in her 2011 book, *The Beekeeper's Lament.*

HANNAH WHITAKER FOR TIME

And now that glue is failing. Around 2006, commercial beekeepers began noticing something disturbing: their honeybees were disappearing. Beekeepers would open their hives and find them full of honeycomb, wax, even honey—but devoid of actual bees. As reports from worried beekeepers rolled in, scientists coined an appropriately apocalyptic term for the mystery malady: colony-collapse disorder (CCD). Suddenly beekeepers found themselves in the media spotlight, the public captivated by the horror-movie mystery of CCD. Seven years later, honeybees are still dying on a scale rarely seen before, and the reasons remain mysterious. One-third of U.S. honeybee colonies died or disappeared during the past winter, a 42% increase over the year before and well above the 10% to 15% losses beekeepers used to experience in normal winters.

Though beekeepers can replenish dead hives over time, the high rates of colony loss are putting intense pressure on the industry and on agriculture. There were just barely enough viable honeybees in the U.S. to service this spring's vital almond pollination in California, putting a product worth nearly $4 billion at risk. Almonds are a big deal—they're the Golden State's most valuable agricultural export, worth more than twice as much as its iconic wine grapes. And almonds, totally dependent on honeybees, are a bellwether of the larger problem. For fruits and vegetables as diverse as cantaloupes, cranberries and cucumbers, pollination can be a farmer's only chance to increase maximum yield. Eliminate the honeybee and agriculture would be permanently diminished. "The take-home message is that we are very close to the edge," says Jeff Pettis, the research leader at the U.S. Department of Agriculture's Bee Research Laboratory. "It's a roll of the dice now."

'THE TAKE-HOME MESSAGE IS THAT WE ARE **VERY CLOSE TO THE EDGE.** IT'S A ROLL OF THE DICE NOW.'
—JEFF PETTIS, USDA

That's why scientists like Pettis are working hard to figure out what's bugging the bees. Agricultural pesticides were an obvious suspect—specifically a popular new class of chemicals known as neonicotinoids, which seem to affect bees and other insects even at what should be safe doses. Other researchers focused on bee-killing pests like the accurately named Varroa destructor, a parasitic mite that has ravaged honeybee colonies since it was accidentally introduced into the U.S. in the 1980s. Others still have looked at bacterial and viral diseases. The lack of a clear culprit only deepened the mystery and the fear, heralding what some greens call a "second silent spring," a reference to Rachel Carson's breakthrough 1962 book, which is widely credited with helping launch the environmental movement. A quote that's often attributed to Albert Einstein became

Dead-out *After repeated colony losses, Doan is ready to get out of the beekeeping business*

HANNAH WHITAKER FOR TIME

a slogan: "If the bee disappears from the surface of the globe, man would have no more than four years to live."

One problem: experts doubt that Einstein ever said those words, but the misattribution is characteristic of the confusion that surrounds the disappearance of the bees, the sense that we're inadvertently killing a species that we've tended and depended on for thousands of years. The loss of the honeybees would leave the planet poorer and hungrier, but what's really scary is the fear that bees may be a sign of what's to come, a symbol that something is deeply wrong with the world around us. "If we don't make some changes soon, we're going to see disaster," says Tom Theobald, a beekeeper in Colorado. "The bees are just the beginning."

Sublethal Effects

IF THE HONEYBEE IS A VICTIM OF NATURAL menaces like viruses and unnatural ones like pesticides, it's worth remembering that the bee itself is not a natural resident of the continent. It was imported to North America in the 17th century, and it thrived until recently because it found a perfect niche in a food system that demands crops at ever cheaper prices and in ever greater quantities. That's a man-made, mercantile ecosystem that not only has been good for the bees and beekeepers but also has meant steady business and big revenue for supermarkets and grocery stores.

Jim Doan has been keeping bees since the age of 5, but the apiary genes in his family go back even further. Doan's father paid his way to college with the proceeds of his part-time beekeeping, and in 1973 he left the bond business to tend bees full time. Bees are even in the Doan family's English coat of arms. Although Jim went to college with the aim of becoming an agriculture teacher, the pull of the beekeeping business was too great.

For a long time, that business was very good. The family built up its operation in the town of Hamlin, in western New York, making money from honey and from pollination contracts with farmers. At the peak of his business, Doan estimates he was responsible for pollinating 1 out of 10 apples grown in New York, running nearly 6,000 hives, one of the biggest such operations in the state. He didn't mind the inevitable stings—"you have to be willing to be punished"—and he could endure the early hours. "We made a lot of honey, and we made a lot of money," he says.

All that ended in 2006, the year CCD hit the mainstream, and Doan's hives weren't spared. That winter, when he popped the covers to check on his bees—tipped off by a fellow beekeeper who experienced one of the first documented cases of CCD—Doan found nothing. "There were hundreds of hives in the backyard and no bees in them," he says. In the years since, he has experienced repeated losses, his bees growing sick and dying. To replace lost hives, Doan needs to buy new queens and split his remaining colonies, which reduces honey production and puts more pressure on his few remaining healthy bees. Eventually it all became unsustainable. In 2013, after decades in the business, Doan gave up. He sold the 112 acres (45 hectares) he owns—land he had been saving to sell after his retirement—and plans to sell his beekeeping equipment as well, provided he can find someone to buy it. Doan is still keeping some bees in the meantime, maintaining a revenue stream while considering his options. Those options include a job at Walmart.

Doan and I walk through his backyard, which is piled high with bee boxes that would resemble filing cabinets, if filing cabinets hummed and vibrated. Doan lends me a protective jacket and a bee veil that covers my face. He walks slowly among the boxes—partly because he's a big guy and partly because bees don't appreciate fast moves—and he spreads smoke in advance, which masks the bees' alarm pheromones and keeps them calm. He opens each box and removes a few frames—the narrowly spaced scaffolds on which the bees build their honeycombs—checking to see how a new population he imported from Florida is doing. Some frames are choked with crawling bees, flowing honey and healthy brood cells, each of which contains an infant bee. But other frames seem abandoned, even the wax in the honeycomb crumbling. Doan lays these boxes—known as dead-outs—on their side.

He used to love checking on his bees. "Now it's gotten to the point where I look at the bees every few weeks, and it scares me," he says. "Will it be a good day, will they be alive, or will I just find a whole lot of junk? It depresses the hell out of me."

Doan's not alone in walking away from such unhappy work. The number of commercial beekeepers has dropped by some three-quarters over the past 15 years, and while all of them may agree that the struggle is just not worth it anymore, they differ on which of the possible causes is most to blame. Doan has settled on the neonicotinoid pesticides—and there's a strong case to be made against them.

The chemicals are used on more than 140 different crops as well as in home gardens, meaning endless chances of exposure for any insect that alights on the treated plants. Doan shows me studies of pollen samples taken from his hives that indicate the presence of dozens of chemicals, including the neonicotinoids. He has testified before Congress about the danger the chemicals pose and is involved in a lawsuit with other beekeepers and with green groups that calls on the Environmental Protection Agency (EPA) to suspend a pair of pesticides in the neonicotinoid class. "The impacts [from the pesticides] are not marginal, and they're not academic," says Peter Jenkins, a

lawyer for the Center for Food Safety and a lead counsel in the suit. "They pose real threats to the viability of pollinators."

American farmers have been dousing their fields with pesticides for decades, meaning that honeybees—which can fly as far as 5 miles (8 km) in search of forage—have been exposed to toxins since well before the dawn of CCD. But neonicotinoids, which were introduced in the mid-1990s and became widespread in the years that followed, are different. The chemicals are known as systematics, which means that seeds are soaked in them before they're planted. Traces of the chemicals are eventually passed on to every part of the mature plant—including the pollen and nectar a bee might come into contact with—and can remain for much longer than other pesticides do. There's really no way to prevent bees from being exposed to some level of neonicotinoids if the pesticides have been used nearby. "We have growing evidence that neonicotinoids can have dangerous effects, especially in conjunction with other pathogens," says Peter Neumann, head of the Institute of Bee Health at the University of Bern in Switzerland.

Ironically, neonicotinoids are actually safer for farmworkers because they can be applied more precisely than older classes of pesticides, which disperse into the air. Bees, however, seem uniquely sensitive to the chemicals. Studies have shown that neonicotinoids attack their nervous system, interfering with their flying and navigation abilities without killing them immediately. "The scientific literature is exploding now with work on sublethal impacts on bees," says James Frazier, an entomologist at Penn State University. The delayed but cumulative effects of repeated exposure might explain why colonies keep dying off year after year despite beekeepers' best efforts. It's as if the bees were being poisoned very slowly.

It's undeniably attractive to blame the honeybee crisis on neonicotinoids. The widespread adoption of these pesticides roughly corresponds to the spike in colony loss, and neonicotinoids are, after all, meant to kill insects. Chemicals are ubiquitous—a recent study found that honeybee pollen was contaminated, on average, with nine different pesticides and fungicides. Best of all, if the problem is neonicotinoids, the solution is simple: ban them. That's what the European Commission decided to do this year, putting a two-year restriction on the use of some neonicotinoids.

SOCIETY IN A BOX
A HONEYBEE'S LIFE, DEATH AND WORLD

Humans have been keeping honeybees for thousands of years, yet the insects still manage to surprise us. Lost in the debate over what is causing the death of bees is how intricately complex their lives are, from the tiniest brood to the virgin queen. After all, what other invertebrate communicates by dance?
—ALEXANDER ACIMAN AND HEATHER JONES

- *The oldest known honeybee specimen dates from 100 million years ago.*
- *The 17th century naturalist Jan Swammerdam discovered that the king bee had ovaries and was, in fact, a queen.*
- *In 1923 scientist Rudolf Steiner predicted that within 100 years artificial cultivation of honeybees would have severe consequences on the bee population.*

THE ANATOMY

Things you may not know about *Apis mellifera*

EYES
Bees have five of them—two large compound eyes and three ocelli used to detect light intensity. A worker's eyes have nearly 7,000 lenses.

WING HOOKS
Hooks enable the bee to attach one of each set of wings together during flight for maximum efficiency.

ELECTROSTATIC CHARGE
A charge on the bee's hair attracts pollen.

THE PROBOSCIS
The airtight, strawlike tube sucks up nectar and also works in reverse to feed offspring from a honey stomach.

MANDIBLE
The jaws help bite and pack pollen as well as shape wax for building honeycomb.

LEGS
Brushes scrape pollen from front to back, where it collects in the pollen basket, a sac attached to the rear leg.

THE BREEDS

There are 20,000 species of bees worldwide, but only six main types are kept commercially:

ITALIAN
RUSSIAN
CARNIOLAN
CAUCASIAN
GERMAN
BUCKFAST

1/12 teaspoon
Amount of honey a worker bee will produce during its short life

$15 billion
Estimated annual amount by which bee pollination increases crop value

In a single trip, a worker bee can visit up to 100 flowers and carry more than half its weight in pollen

THE BASICS

	WORKER	DRONE	QUEEN
DUTIES	Construction, storage, keeping the nursery, guarding, caretaking, scouting and foraging.	Mates with a virgin queen in midair. Can fly backward, rotate and flip.	Lays up to 1,500 eggs a day, possibly more. Secretes pheromones to control workers.
LIFE SPAN	20–30 days	Dies after mating	3–7 years

WINGS
A bee has two sets of wings. Rapid flapping generates warmth and evaporates water from nectar to make honey.

HONEY STOMACH
A second reservoir where nectar is temporarily stored before being regurgitated.

STING
When a bee stings, a barb prevents the stinger from being pulled out; the bee then tears its abdomen while freeing itself before dying.

WAX PLATES
Bees secrete wax beneath plates on their abdomen and use it to build honeycomb.

VENOM
The unique mixture of chemicals that causes a sting to hurt may play a role in stopping the spread of HIV, which venom has been shown to destroy.

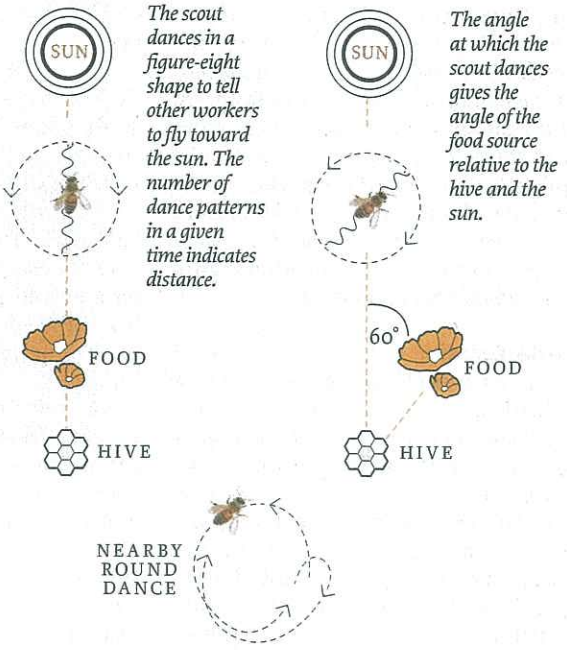
In order to produce 1 lb. (0.4 kg) of honey, hive workers fly a collective 55,000 miles (89,000 km)

THE HIVE

A colony typically comprises 20,000 to 30,000 bees. Although it has long been believed that bees hibernate in the winter, the colony creates a winter ecosystem inside the hive and lives off honey, with the bees maintaining warmth by working their wings. Middle-aged worker bees build by attaching each comb to the walls of the hive—a process that often requires more than 2 lb. (1 kg) of wax.

THE DANCE

When a scout worker has successfully located food, it alerts its fellow foragers about the food's location with a series of dance moves. Through the number of turns, the duration of the dance and the moves themselves, the scout can communicate the distance to the food, the angle of the food to the sun and whether it is near or far.



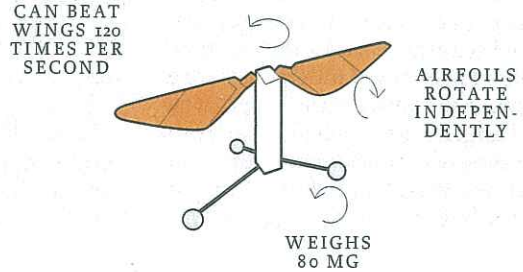
The scout dances in a figure-eight shape to tell other workers to fly toward the sun. The number of dance patterns in a given time indicates distance.

The angle at which the scout dances gives the angle of the food source relative to the hive and the sun.

THE FUTURE

THE ROBOBEE

Harvard's School of Engineering and Applied Sciences conducted the first successful flight of a life-size robotic fly in 2007. The lab has received $10 million in grant money from the National Science Foundation to build a network of autonomous artificial bees.



APPLICATIONS

- SEARCH AND RESCUE
- ARTIFICIAL POLLINATION
- COVERT SURVEILLANCE
- HIGH-RESOLUTION WEATHER AND CLIMATE MAPPING
- TRAFFIC MONITORING

Sources: Washington University School of Medicine; PBS; USDA; Roger A. Morse and Nicholas W. Calderone, Cornell University; *Bee*/Rose-Lynn Fisher; *National Geographic;* Harvard School of Engineering and Applied Sciences; *Encyclopaedia Britannica; Bees*/Lectures by Rudolf Steiner; North Carolina State College of Agriculture and Life Sciences; University of Illinois at Urbana-Champaign

Photograph by Tom Schierlitz for TIME

But while the EPA is planning to review neonicotinoids, a European-style ban is unlikely—in part because the evidence is still unclear. Beekeepers in Australia have been largely spared from CCD even though neonicotinoids are used there, while France has continued to suffer bee losses despite restricting the use of the pesticides since 1999. Pesticide makers argue that actual levels of neonicotinoid exposure in the field are too low to be the main culprit in colony loss. "We've dealt with insecticides for a long time," says Randy Oliver, a beekeeper who has done independent research on CCD. "I'm not thoroughly convinced this is a major issue."

Hostile Terrain

EVEN IF PESTICIDES ARE A BIG PART OF THE bee-death mystery, there are other suspects. Beekeepers have always had to protect their charges from dangers such as the American foulbrood—a bacterial disease that kills developing bees—and the small hive beetle, a pest that can infiltrate and contaminate colonies. Bloodiest of all is the multidecade war against the Varroa destructor, a microscopic mite that burrows into the brood cells that host baby bees. The mites are equipped with a sharp, two-pronged tongue that can pierce a bee's exoskeleton and suck its hemolymph—the fluid that serves as blood in bees. And since the Varroa can also spread a number of other diseases—they're the bee equivalent of a dirty hypodermic needle—an uncontrolled mite infestation can quickly lead to a dying hive.

The Varroa first surfaced in the U.S. in 1987—likely from infected bees imported from South America—and it has killed billions of bees since. Countermeasures used by beekeepers, including chemical miticides, have proved only partly effective. "When the Varroa mite made its way in, it changed what we had to do," says Jerry Hayes, who heads Monsanto's commercial bee work. "It's not easy to try to kill a little bug on a big bug."

Other researchers have pointed a finger at fungal infections like the parasite *Nosema ceranae*, possibly in league with a pathogen like the invertebrate iridescent virus. But again, the evidence isn't conclusive: some CCD-afflicted hives show evidence of fungi or mites or viruses, and others don't. Some beekeepers are skeptical that there's an underlying problem at all, preferring to blame CCD on what they call PPB—piss-poor beekeeping, a failure of beekeepers to stay on top of colony health. But while not every major beekeeper has suffered catastrophic loss, colony failures have been widespread for long enough that it seems perverse to blame the human victims. "I've been keeping bees for decades," says Doan. "It's not like I suddenly forgot how to do it in 2006."

There's also the simple fact that beekeepers live in a country that is becoming inhospitable to honeybees. To survive, bees need forage, which means flowers and wild spaces. Our industrialized agricultural system has conspired against that, transforming the countryside into vast stretches of crop monocultures—factory fields of corn or soybeans that are little more than a desert for honeybees starved of pollen and nectar. Under the Conservation Reserve Program (CRP), the government rents land from farmers and sets it aside, taking it out of production to conserve soil and preserve wildlife. But as prices of commodity crops like corn and soybeans have skyrocketed, farmers have found that they can make much more money planting on even marginal land than they can from the CRP rentals. This year, just 25.3 million acres (10.2 million hectares) will be held in the CRP, down by one-third from the peak in 2007 and the smallest area in reserve since 1988.

'WE CAN REPLACE THE BEES, BUT **WE CAN'T REPLACE BEEKEEPERS** WITH 40 YEARS OF EXPERIENCE.'

—TIM TUCKER, VICE PRESIDENT, AMERICAN BEEKEEPING FEDERATION

Lonely Spring

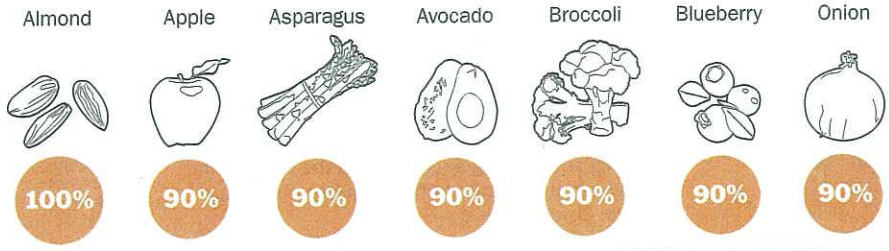
FOR ALL THE ENEMIES THAT ARE MASSING against honeybees, a bee-pocalypse isn't quite upon us yet. Even with the high rates of annual loss, the number of managed honeybee colonies in the U.S. has stayed stable over the past 15 years, at about 2.5 million. That's still significantly down from the 5.8 million colonies that were kept in 1946, but that shift had more to do with competition from cheap imported honey and the general rural depopulation of the U.S. over the past half-century. (The number of farms in the U.S. fell from a peak of 6.8 million in 1935 to just 2.2 million today, even as food production has ballooned.) Honeybees have a remarkable ability to regenerate, and year after year the beekeepers who remain have been able to regrow their stocks after a bad loss. But the burden on beekeepers is becoming unbearable. Since 2006 an estimated 10 million beehives have been lost, at a cost of some $2 billion. "We can replace the bees, but we can't replace beekeepers with 40 years of experience," says Tim Tucker, the vice president of the American Beekeeping Federation.

As valuable as honeybees are, the food system wouldn't collapse without them. The backbone of the world's diet—grains like corn, wheat and rice—is self-pollinating. But our dinner plates would be far less colorful, not to mention far less nutritious, without blueberries, cherries, watermelons, lettuce and the scores of other plants that would be challenging to raise commercially without honeybee pollination. There could be replacements. In southwest China, where wild bees have all but died out thanks to massive pesticide

HANNAH WHITAKER FOR TIME (2)

THE IMPACT ON THE FARM

Although many crops are only partially dependent on bee pollination, others, like the almond, cannot get by without it. According to the USDA, one-third of the food in our diet relies to some extent on bee pollination.



Bee bust *Doan believes pesticides are chiefly responsible for the high death rates in his honeybee operation*

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use, farmers laboriously hand-pollinate pear and apple trees with brushes. Scientists at Harvard are experimenting with tiny robobees that might one day be able to pollinate autonomously. But right now, neither solution is technically or economically feasible. The government could do its part by placing tighter regulations on the use of all pesticides, especially during planting season. There needs to be more support for the CRP too to break up the crop monocultures that are suffocating honeybees. One way we can all help is by planting bee-friendly flowers in backyard gardens and keeping them free of pesticides. The country, says Dennis vanEngelsdorp, a research scientist at the University of Maryland who has studied CCD since it first emerged, is suffering from a "nature deficit disorder"—and the bees are paying the price.

But the reality is that barring a major change in the way the U.S. grows food, the pressure on honeybees won't subside. There are more than 1,200 pesticides currently registered for use in the U.S.; nobody pretends that number will be coming down by a lot. Instead, the honeybee and its various pests are more likely to be changed to fit into the existing agricultural system. Monsanto is working on an RNA-interference technology that can kill the Varroa mite by disrupting the way its genes are expressed. The result would be a species-specific self-destruct mechanism—a much better alternative than the toxic and often ineffective miticides beekeepers have been forced to use. Meanwhile, researchers at Washington State University are developing what will probably be the world's smallest sperm bank—a bee-genome repository that will be used to crossbreed a more resilient honeybee from the 28 recognized subspecies of the insect around the world.

Already, commercial beekeepers have adjusted to the threats facing their charges by spending more to provide supplemental feed to their colonies. Supplemental feed raises costs, and some scientists worry that replacing honey with sugar or corn syrup can leave bees less capable of fighting off infections. But beekeepers living adrift in a nutritional wasteland have little choice. The beekeeping business may well begin to resemble the industrial farming industry it works with: fewer beekeepers running larger operations that produce enough revenue to pay for the equipment and technologies needed to stay ahead of an increasingly hostile environment. "Bees may end up managed like cattle, pigs and chicken, where we put them in confinement and bring the food to them," says Oliver, the beekeeper and independent researcher. "You could do feedlot beekeeping."

That's something no one in the beekeeping world wants to see. But it may be the only way to keep honeybees going. And as long as there are almonds, apples, apricots and scores of other fruits and vegetables that need pollinating—and farmers willing to pay for the service—beekeepers will find a way.

So if the honeybee survives, it likely won't resemble what we've known for centuries. But it could be worse. For all the recent attention on the commercial honeybee, wild bees are in far worse shape. In June, after a landscaping company sprayed insecticide on trees, 50,000 wild bumblebees in Oregon were killed—the largest such mass poisoning on record. Unlike the honeybee, the bumblebee has no human caretakers. Globally, up to 100,000 animal species die off each year—nearly every one of them without fanfare or notice. This is what happens when one species—that would be us—becomes so widespread and so dominant that it crowds out almost everything else. It won't be a second silent spring that dawns; we'll still have the buzz of the feedlot honeybee in our ears. But humans and our handful of preferred species may find that all of our seasons have become lonelier ones. ■