May 4, 2020

OPP Docket, U.S. EPA Docket Center (EPA/DC), (28221T)
1200 Pennsylvania Ave. NW
Washington, DC 20460-0001

RE: Petition to Revoke All Neonic Tolerances and Comments Regarding Dietary Exposure

Pursuant to 21 U.S.C. § 346a(d)(1)(A), the Natural Resources Defense Council (NRDC) submits this petition to revoke all tolerances for residues of neonicotinoid pesticides ("neonics") on or in food. We request that EPA respond to this petition as soon as practicable and, in any event, no later than the interim registration review decision for neonics. NRDC also submits these comments in opposition to the Environmental Protection Agency's (EPA) proposed interim registration review decisions, which would permit continued, widespread use of neonics.

These comments are submitted to the following dockets:

Imidacloprid	(EPA-HQ-OPP-2008-0844)
Thiamethoxam	(EPA-HQ-OPP-2011-0581)
Clothianidin	(EPA-HQ-OPP-2011-0865)
Acetamiprid	(EPA-HQ-OPP-2012-0329)
Dinotefuran	(EPA-HQ-OPP-2011-0920)

NRDC incorporates by reference, in full, all studies and documents cited in this petition.

Current neonic tolerances violate the Food, Drug, and Cosmetics Act, 21 U.S.C. § 346a, as amended by the Food Quality Protection Act (FQPA), 110 Stat. 1489 (Aug. 3, 1996). "The Administrator may establish or leave in effect a tolerance for a pesticide chemical residue in or on a food only if the Administrator determines that the tolerance is safe." 21 U.S.C. § 346a(b)(2)(A)(i). EPA's current tolerances permit widespread exposure to neonics—demonstrated developmental neurotoxicants—at levels that are not "safe" for the American population.

Five failings in EPA's analysis underly these unlawful tolerances. EPA fails to: (1) use the most sensitive endpoint and appropriate uncertainty factors when calculating the reference dose; (2) retain the FQPA 10X child safety factor; (3) assess the cumulative impacts of exposure to the neonic class; (4) assess aggregate effects of exposure to neonics and all degradates; and (5) conduct an acute dietary risk assessment that accounts for risks to high-exposure individuals. Taking these factors properly into account, EPA must revoke all tolerances for neonics. Moreover, EPA's unlawful analysis renders its determination that neonics satisfy the standard under the Federal Insecticide, Fungicide, and Rodenticide Act, 7 U.S.C. § 136a, arbitrary and unsupported by substantial evidence.

NATURAL RESOURCES DEFENSE COUNCIL

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I. LEGAL BACKGROUND

a. FIFRA and the FDCA

Two statutes govern the use and sale of pesticides: the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), 7 U.S.C. § 136 et seq., and the Federal Food, Drug, and Cosmetic Act ("Food Act" or FDCA), 21 U.S.C. § 346a. No pesticide may be sold or used unless it is registered with EPA under FIFRA. 7 U.S.C. § 136a(a). Before registering a pesticide, EPA must determine that it will "perform its intended function without unreasonable adverse effects on the environment" ("FIFRA standard"). *Id.* § 136a(c)(5)(C). The term "unreasonable adverse effects on the environment" means (1) "any unreasonable risk to man or the environment, taking into account the economic, social, and environmental costs and benefits of the use of any pesticide," or (2) "a human dietary risk from residues that result from a use of a pesticide in or on any food inconsistent with the standard under [the FDCA, 21 U.S.C. § 346a]." 7 U.S.C. § 136(bb).

Under the FDCA, EPA must establish tolerances for pesticide residues on food. Tolerances are maximum amounts of a pesticide that can be found on a particular food, subject to EPA's determination that the amount is "safe." 21 U.S.C. § 346a(b)(2)(A)(i). This means "there is a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information." *Id.* § 346a(b)(2)(A)(ii). In addition to the cost-benefit analysis described in FIFRA, the FIFRA standard requires EPA to assess a pesticide product's compliance with this safety standard, which is purely health-protective. 7 U.S.C. § 136(bb).

During registration review, EPA prepares risk and benefit assessments to assess "any changes that may have occurred since the Agency's last registration decision" and determine whether those changes affect the registration's compliance with the FIFRA standard. 40 C.F.R. § 155.53(a). Based on those assessments, EPA ultimately issues a registration review decision, which is "the Agency's determination whether a pesticide meets, or does not meet, the standard for registration in FIFRA." *Id.* § 155.57. As it has for neonics, EPA may also issue an interim registration review decision before its final decision to "require new risk mitigation measures, impose interim risk mitigation measures, identify data or information required to complete the review, and include schedules for submitting the required data, conducting the new risk assessment and completing the registration review." *Id.* § 155.56. An interim registration review decision is itself final agency action.

b. The FQPA

In 1996, Congress passed the FQPA, which amended the Food Act to protect sensitive populations, such as pregnant mothers, fetuses, and young children, from dangerous chemicals in food and the environment. To this end, the FQPA requires EPA to take three steps when establishing tolerances for pesticide residues under the Food Act. First, it requires EPA to consider "aggregate exposure" of consumers to pesticide residues from all dietary and other non-occupational exposure sources. 21 U.S.C. § 346a(b)(2)(D)(vi). Second, EPA must consider "cumulative effects of such residues and other substances that have a common mechanism of

toxicity." *Id.* § 346a(b)(2)(D)(v). Third, the FQPA requires EPA to apply an "additional tenfold margin of safety . . . to take into account potential pre- and post-natal toxicity and completeness of the data with respect to exposure and toxicity to infants and children." *Id.* § 346a(b)(2)(C)(ii)(II). EPA may use a different safety factor if it finds, "on the basis of reliable data, such margin will be safe for infants and children." *Id.*

II. FACTUAL BACKGROUND

a. Infants and Children Are Uniquely Vulnerable to Exposure to Neurotoxic Agents

i. The nicotinic acetylcholine receptor plays a central role during the extraordinarily complex development of the central nervous system

The development of the brain and spinal cord—together called the central nervous system, or "CNS"—is extraordinarily complex, continuing throughout fetal and infant development. It is a tightly coordinated process of rapid cellular division, growth, differentiation, migration, networking, and maturation. Each cell receives information from a previous one, and then initiates a cascade of cellular events, which occurs in five stages:[1]

1. Neurogenesis – differentiation of embryonic cells to create neurons.
2. Migration – the movement of cells to form the final architecture of the brain and nervous system. Thyroid hormones, shown in several vertebrate species to be disrupted by neonics (detailed elsewhere in these comments), are critical to successful timing and direction of neuronal migration.[2] Errors in this step will reverberate through the remaining steps of the process of brain and nervous system maturation and function.
3. Synaptogenesis – forming communication points, called synapses, between each neuron and its target cell, either another neuron or a muscle cell. The synapse is a small gap, where proteins called 'neurotransmitters' are released from the 'pre-synaptic' neuron, travel across the gap, and contact the appropriate receptor on the 'post-synaptic' target cell, to trigger a cascade of cellular events such as muscle cell contraction.
4. Pruning back about half of the quadrillion or so synapses that have formed between birth and age two. This 'plasticity' allows for learning to shape the brain. Since the brain is molded according to the environment it experiences, this is also how harmful chemical exposures during development can lead to adverse brain structure and function;

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[1] Sandra Steingraber, *Raising Elijah*, pp. 215-217, Cambridge, MA: Da Capo Press (2011).

[2] Berheim EH, Jenks JA, Lundgren JG, Michel ES, Grove D, Jensen WF, *Effects of Neonicotinoid Insecticides on Physiology and Reproductive Characteristics of Captive Female and Fawn White-tailed Deer*, 9 (1) Sci. Rep. 4534 (Mar. 14, 2019), doi:10.1038/s41598-019-40994-9, https://go.nature.com/2sgOOHb; Wang Y, Xu P, Chang J, Li W, Yang L, Tian H, *Unraveling the Toxic Effects of Neonicotinoid Insecticides on the Thyroid Endocrine System of Lizards*, 258 Environ. Pollut. 113731 (Mar. 2020), doi: 10.1016/j.envpol.2019.113731, https://bit.ly/3desUGB. Pandey SP, Mohanty B., *The Neonicotinoid Pesticide Imidacloprid and the Dithiocarbamate Fungicide Mancozeb Disrupt the Pituitary-Thyroid Axis of a Wildlife Bird*, 122 Chemosphere 227-234 (Mar. 2015), doi: 10.1016/j.chemosphere.2014.11.061, https://go.nature.com/2Q1I9Zf.

5. Myelination is one of the final steps, when fatty glial cell, wraps around the long axons of the neuron cells, acting just as insulation around a wire, to speed up the transmission along the neuron by preventing electric charge from leaking out (in the form of charged ions like sodium, potassium, calcium, and chloride).[3]

These five stages occur in sequential order, moving through the brain like a pulse or wave, so that the first and fifth stages may be occurring at the same time, but in different locations. Like an orchestra or ballet, every cell and molecule must do its part at the right time and in the right place, or those that are supposed to come next will not receive their proper cues and so on. The timing and location of cell-to-cell communication is a crucial component.

Cell communication in the brain is carried out by proteins called neurotransmitters, substances that transmit nerve impulses throughout the central and peripheral nervous systems (CNS, PNS). One of the most widespread neurotransmitters in the human body is acetylcholine (ACh), used by neurons in the PNS to contract skeletal muscle (voluntary muscle) during body movement, contract smooth muscle (involuntary muscle) to increase digestion and urination, dilate blood vessels, increase bodily secretions, and regulate heart rate.[4] Too much ACh can over-stimulate muscle contractions, causing spasms and seizures. In the CNS (brain and spinal cord), ACh activity supports motivation, attention, memory, learning, and REM sleep. Severe depletion of ACh is associated with Alzheimer's disease. Its most widespread receptor is the nicotinic receptor (nAChR), the target of neonicotinoid pesticides. Appropriate activation of the nAChR is required for healthy development and function of the nervous system.[5] Disruption of this system, such as with an influx of nicotine which triggers the receptor inappropriately, has been demonstrated in animal models to perturb the orderly process by which neurons become fully functional, including growth, migration, and the formation of synapses (synaptogenesis) between neurons and their target cells.

During subsequent stages of prenatal development, the nAChR functions to form sensory, memory, and muscle functioning through mediating the proper development of critical areas of the brain such as the cortex, thalamus, and cerebellum, which are dense with nAChRs.[6]

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[3] Enes J, Haburčák M, Sona S, Gerard N, Mitchell AC, Fu W, Birren SJ, *Satellite Glial Cells Modulate Cholinergic Transmission Between Sympathetic Neurons,* 15 (2) PLoS One (Feb. 4, 2020), e0218643, doi:10.1371/journal.pone.0218643, https://bit.ly/2xxQC1v; Allen NJ, *Role of Glia in Developmental Synapse Formation*, 23 (6) Curr. Opin. Neurobiol., 1027-33 (Dec. 2016), doi: 10.1016/j.conb.2013.06.004, https://bit.ly/35uQPPl; Corty MM, Freeman MR, *Cell Biology in Neuroscience: Architects in Neural Circuit Design: Glia Control Neuron Numbers and Connectivity*, 203 (3) J. Cell Biol., 395-405 (Nov. 11, 2013), doi: 10.1083/jcb.201306099, https://bit.ly/35v6zBX.

[4] Cherry K, medically reviewed by Claudia Chaves, MD, *Discovery and Functions of Acetylcholine* (Oct. 9, 2019), https://bit.ly/2zLSGDE; Encyclopaedia Britannica, Acetylcholine, (Dec. 2019), https://bit.ly/35pt37s.

[5] Blood-Siegfried J, Rende EK, *The Long-Term Effects of Prenatal Nicotine Exposure on Neurologic Development*, 55 (2) J. Midwifery Women's Health 143-52 (Mar.-Apr. 2010), doi: 10.1016/j.jmwh.2009.05.006, https://bit.ly/2W2tGAY.

[6] *Id.*

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Interference with neurotransmitters and associated receptors can cause permanent neurological or other developmental impairment.

ii. Exposure to neurotoxic chemicals, even in small doses or for short durations, during 'critical windows,' interferes with development and can lead to lasting cognitive and behavioral deficits

Scientists describe the period of early development of the brain and nervous system as a 'critical window' of sensitivity, when the system is undergoing rapid cell growth, migration, differentiation, nutrition uptake, and formation of the final organ structure. Because neurodevelopment progresses like a wave through the brain and spinal cord, exposure to neurotoxic agents may produce different neurological effects under different test conditions, and at different doses, even in the same species, depending on when the toxic exposure occurs, and how long it lasts. Experts note, "chronic exposure throughout pregnancy [to nicotine] will affect many different functions in the developing brain, whereas exposure that is limited to a specific time of pregnancy may only affect the specific functions during that precise interval."[7] For this reason, the entire period of neurodevelopment is considered a critical window of increased sensitivity to toxic chemicals.

Experts warn that exposure to harmful chemicals at any time during neurodevelopment, even at low levels or for only a short time, may lead to long-lasting physical, cognitive, and behavioral impairments.[8] This is described in detail regarding pesticides in the landmark 1993 National Academies of Science report, *Pesticides in the Diets of Infants and Children*. That report noted, "[s]tudies in animals suggest that the nature of an injury is determined by the stage of brain development at the time of exposure rather than by the relationship of the insult to the time of the birth event."[9] That is, it is not only the dose that makes the poison, but also the timing

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[7] *Id.*

[8] Heindel JJ, Balbus J, Birnbaum L, Brune-Drisse MN, Grandjean P, Gray K, Landrigan PJ, Sly PD, Suk W, Cory Slechta D, Thompson C, Hanson M, *Developmental Origins of Health and Disease: Integrating Environmental Influences*, 156 (10) Endocrinology 3416-21 (Oct. 2015), doi: 10.1210/EN.2015-1394, https://bit.ly/3b3ibNZ; Bennett D, Bellinger DC, Birnbaum LS, Bradman A, Chen A, Cory-Slechta DA, Engel SM, Fallin MD, Halladay A, Hauser R, Hertz-Picciotto I, Kwiatkowski CF, Lanphear BP, Marquez E, Marty M, McPartland J, Newschaffer CJ, Payne-Sturges D, Patisaul HB, Perera FP, Ritz B, Sass J, Schantz SL, Webster TF, Whyatt RM, Woodruff TJ, Zoeller RT, Anderko L, Campbell C, Conry JA, DeNicola N, Gould RM, Hirtz D, Huffling K, Landrigan PJ, Lavin A, Miller M, Mitchell MA, Rubin L, Schettler T, Tran HL, Acosta A, Brody C, Miller E, Miller P, Swanson M, Witherspoon NO, American College of Obstetricians and Gynecologists (ACOG), Child Neurology Society, Endocrine Society, International Neurotoxicology Association, International Society for Children's Health and the Environment, International Society for Environmental Epidemiology, National Council of Asian Pacific Islander Physicians, National Hispanic Medical Association, National Medical Association, *Project TENDR: Targeting Environmental Neuro-Developmental Risks The TENDR Consensus Statement*, 124 (7) Environ Health Perspect. A118-22 (Jul. 1, 2016), doi: 10.1289/EHP358, https://bit.ly/2W1UgtR; Steingraber S, *Living Downstream: An Ecologist's Personal Investigation of Cancer and the Environment*, Da Capo Press, Cambridge, MA (2010).

[9] National Research Council (US) Committee on Pesticides in the Diets of Infants and Children, *Pesticides in the Diets of Infants and Children*, Washington (DC): National Academies Press (US); (1993), https://bit.ly/2SrudKo.

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during critical windows of development. NRDC incorporates by reference the text of the 1993 NAS report into this petition.

The report described a number of key characteristics that make early life stages so vulnerable to neurotoxic pesticides:

- On a per-body-weight basis, a child's exposure to pesticides is much greater than an adult, because, pound-for-pound, children eat more, drink more, and breathe more air than adults;
- Children spend more time than adults in close contact with surfaces treated with pesticides, including floors, lawns and playgrounds, and family pets;
- The blood-brain-barrier does not fully form until birth, exposing this critical organ to any pesticides or other contaminants in the fetal circulation;[10]
- During fetal and early childhood, the body organs and systems are developing more rapidly than at any other time over a person's lifespan. This has two implications: first, along with the intake of nutrition, cells will absorb contaminants in the blood and air supply; second, the rapid activity of neurons and other cells means that perturbations or errors during this time are likely to be hard-wired into the brain and nervous systems and cannot be undone or corrected later in life;[11]
- Cellular and metabolic systems that detoxify and excrete chemicals are not fully functional during early development; and
- The longer life span of a child compared to an adult allows more time for delayed adverse effects to manifest.

Fetal development may be particularly and permanently harmed by even low-level or short-term neurotoxic exposures. During this time, the fetus has little to no protection against toxic chemicals. The placenta, through which the fetus receives all of its nutrition via the mother's blood supply, is unable to fully block the passage of many environmental toxicants, including neonic pesticides, from flooding directly into the fetal circulation. Once in the fetal circulation, nothing protects the brain and other sensitive organs from being awash in any harmful chemicals that enter along with the necessary nutrients. Researchers have measured over 200 industrial chemical pollutants in umbilical cord blood of newborn babies, including many pesticides, carcinogens, and neurotoxic agents, demonstrating their presence in the fetal circulation.[12]

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[10] Serlin Y, Shelef I, Knyazer B, Friedman A, *Anatomy and Physiology of the Blood-Brain Barrier*, 38 Semin. Cell Dev. Biol. 2-6 (Feb. 2015), doi: 10.1016/j.semcdb.2015.01.002, https://bit.ly/2WjhuKM.

[11] Changes to the body plan are only possible during embryonic development, when errors or disruptions are hard-wired. Later, cell growth and division are slowed or stopped, so changes are no longer possible. If developmental alterations are too dramatic, they are often incompatible with life, leading to fetal resorptions or still births.

[12] Grandjean P, Landrigan PJ, *Neurobehavioural Effects of Developmental Toxicity*, 13 (3) Lancet Neurol. 330-8 (Mar. 2014), doi: 10.1016/S1474-4422(13)70278-3, https://bit.ly/3dcIBy4; Needham LL, Grandjean P, Heinzow B, Jørgensen PJ, Nielsen F, Patterson DG Jr, Sjödin A, Turner WE, Weihe P, *Partition of Environmental Chemicals*

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The nervous system is integrated throughout the entire body, both physically and functionally. The system may look 'normal' to the naked eye, or even under a microscope, but may be unable to perform its duties properly when challenged with specific circumstances. For example, many of the low-level effects of prenatal exposure to lead can go largely undetected in a rodent study, but result in behavioral changes that make classroom learning difficult for a child.

b. Neonics Are Neurotoxic Agents

i. Mechanism of developmental neurotoxicity in insects and humans

The popular but false narrative is that because neonics have a lower affinity for vertebrate receptors than invertebrate receptors, they kill insects, but have a 'favorable toxicological profile' for fish, birds, mammals, and people.[13] This perceived lower affinity for the vertebrate receptor is due to the specific receptor subunit that the neonic pesticides bind—the α4β2 subunit—which is in all insect nAChRs, but in a smaller fraction of the receptors in vertebrates.[14] However, the α4β2 subunit is the most commonly expressed subtype in the mammalian brain and CNS, and has a particularly high affinity for nicotine, and presumably therefore also the neonic pesticides.[15] The cortex, thalamus, and cerebellum are all areas of the brain shown to be heavily populated with nAChRs that contain the α4β2 subunit.[16]

Perhaps even more concerning is the manner in which neonics harm nAChRs. The appropriate ligand for these receptors, acetylcholine, binds transiently and then is quickly released. Neonics, however, bind permanently to insect nAChRs, causing continuous stimulation of the neuron until its death.[17] All the neonic pesticides exhibit this mechanism of toxicity—a neurotoxic mechanism—in both insects and mammals.[18] "The mammalian toxicity of neonicotinoids … correlates with agonist action and binding affinity at the vertebrate α4β2

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between Maternal and Fetal Blood and Tissues, 45 (3) Environ Sci Technol. 1121-6 (Feb. 1, 2011), doi: 10.1021/es1019614, https://bit.ly/3fn4zR4; Commonweal & Environmental Working Group, *Body Burden—the Pollution in Newborns: A Benchmark Investigation of Industrial Chemicals, Pollutants and Pesticides in Umbilical Cord Blood* (2005), https://bit.ly/2VX6CTU.

[13] Tomizawa M, Casida JE, *Neonicotinoid Insecticide Toxicology: Mechanisms of Selective Action*, 45 Ann. Rev. Pharmacol. Toxicol. 247-68 (2005), https://bit.ly/2Yoqu4a.

[14] Tomizawa & Casida (2005), https://bit.ly/2Yoqu4a.

[15] Posadas I, López-Hernández B, Ceña V, *Nicotinic receptors in neurodegeneration*, 11 (3) Curr. Neuropharmacol. 298-314 (May 2013), doi: 10.2174/1570159X11311030005, https://bit.ly/2W0wHl6.

[16] *Id.*

[17] EPA, Clothianidin fact sheet. Mechanism of Pesticidal Action at 17 (2003), https://bit.ly/2WnbXmt; Tomizawa M, Casida JE, *Selective toxicity of neonicotinoids attributable to specificity of insect and mammalian nicotinic receptors*, 48 Annu Rev Entomol. 339-64 (2003), https://bit.ly/2SxuFXs.

[18] *Id.*

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nAChR, the primary target in the brain."[19] In mammals and other vertebrates, prolonged excitation of nerve and muscle cells can lead to delayed or lasting toxic effects.[20]

In summary, all the neonics are neurotoxic; their target receptor is widespread in the mammalian nervous system; and that receptor plays a critical role in the development and function of the mammalian brain and nervous system. This mechanism of developmental neurotoxicity, prolonged binding to the nAChR, is shared across all the neonics. Accordingly, exposure to neonic pesticides during critical windows of brain development poses a risk of developmental disabilities.

ii. Neonic poisoning elicits neurotoxic effects

Neonic poisoning shares the same symptoms as poisoning by organophosphate pesticides (OP)—which under FQPA were slated for cancellation and phase-out by 2006 in homes, lawns and gardens, and on many food crops that are kid's favorites due to both acute poisoning incidences and risk of developmental harm to pregnant women and children. EPA lists the dramatic reduction in OP uses, and the resultant reduction in human poisonings and exposures, as one of the most important accomplishments of FQPA for protecting children.[21] Neonics operate by a similar mechanism of toxicity and exhibit similar effects on the nervous system, yet EPA continues to approve their use.

EPA's Pesticide Poisoning Handbook lists the signs and symptoms of neonic poisoning: "Patients have presented with disorientation, confusion and agitation – severe enough to require sedation – headache, drowsiness, dizziness, weakness, tremor and, in some situations, loss of consciousness. No seizures have been reported, and chronic residual neuropsychiatric effects have not been studied."[22] Notably, EPA does not identify symptoms specific to any particular neonic, but says that the effects of poisoning is applicable to the follow common group: acetamiprid, clothianidin, dinotefuran, imidacloprid, thiacloprid, and thiamethoxam. EPA's treatment of neonics as a common group when considering the shared signs and symptoms of

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[19] Tomizawa & Casida (2005), https://bit.ly/2Yoqu4a.

[20] Sánchez-Bayo F, Tennekes HA, *Time-Cumulative Toxicity of Neonicotinoids: Experimental Evidence and Implications for Environmental Risk Assessments*, 17 (5) Int J Environ Res Public Health. (Mar. 3, 2020), doi: 0.3390/ijerph17051629, https://bit.ly/2xuV68W; Posadas et al. (2013), doi: 10.2174/1570159X11311030005, https://bit.ly/3dlzCuJ; Simon-Delso N, Amaral-Rogers V, Belzunces LP, Bonmatin JM, Chagnon M, Downs C, Furlan L, Gibbons DW, Giorio C, Girolami V, Goulson D, Kreutzweiser DP, Krupke CH, Liess M, Long E, McField M, Mineau P, Mitchell EA, Morrissey CA, Noome DA, Pisa L, Settele J, Stark JD, Tapparo A, Van Dyck H, Van Praagh J, Van der Sluijs JP, Whitehorn PR, Wiemers M., *Systemic Insecticides (Neonicotinoids and Fipronil): Trends, Uses, Mode of Action and Metabolites*, 22 (1) Environ. Sci. Pollut. Res. Int. 5-34 (Jan. 2015), doi: 10.1007/s11356-014-3470-y, https://bit.ly/3djKARn.

[21] *See* Debbie Edwards, Director, SRRD/OPP, Presentation on Registration and Tolerance Reassessment to the Pesticide Program Dialogue Committee (Nov. 8, 2006), https://bit.ly/35rclV9.

[22] EPA, Recognition and Management of Pesticide Poisonings: 6th Edition, Chapter 9 Other Insecticides and Acaricides (2013), https://bit.ly/2KX4Fkh.

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poisoning is evidence that EPA acknowledges that exposure to two or more different neonics will lead to amplification of a shared suite of poisoning symptoms, thus supporting their consideration in a cumulative assessment group. *See infra*, Section IV.

EPA has identified an alarming number of incidences of severe human poisoning from neonics in the U.S., largely from intentional exposures, lawn and garden products, and as a flea-treatment for family cats and dogs. Under FIFRA Sec. 6(a)(2) reporting requirements, EPA identified roughly 1,630 incidents of imidacloprid poisoning over a 10-year period, about 160/year.[23] Non-agricultural uses of neonics have led to poisonings of people, including, but not limited to, the following adverse effects according to incident poisoning reports:[24]

- Clothianidin – numbness, chest pain, headache, muscle weakness and tremors, shortness of breath, sore throat, coughing, skin rash and itching, tachycardia (rapid heart rate), blurred vision, and abdominal pain;
- Imidacloprid – rash, muscle tremor, difficulty breathing, vomiting, wheezing, lock jaw, memory loss, and renal failure; and
- Thiamethoxam – throat irritation, skin irritation and rash, fever, numbness, dizziness, diarrhea, and sweating (and note that the major metabolite of thiamethoxam is clothianidin).

Globally, there are medical reports and other documented cases of human poisonings with effects including confusion, convulsions, and coma.[25] These are especially concerning given their serious medical risks, and the lack of any clear antidote or treatment.

For occupational poisoning incidents, EPA reports that: "A query of SENSOR-Pesticides (1998 – 2013) identified 16 cases involving thiamethoxam. Eleven cases involved multiple active ingredients and five cases involved a single active ingredient. One case was high in severity, three cases were moderate in severity, and 12 cases were low in severity. Four of the cases were coded as occupational in nature. The one high severity thiamethoxam incident occurred in Michigan in 2011 and involved an adult male who was not wearing the required PPE (gloves). He experienced *a rash that lasted for more than 1.5 months and swelling in his neck* that altered his voice" (Clothianidin and Thiamethoxam PID, p. 24-25; emphasis added). This is

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[23] EPA, Office of Pesticide Programs Incident Data System, Neonicotinoid incident reports for 01/01/2009 to 04/04/2019. Received by NRDC via Freedom of Information Act Request No. EPA-HQ-2019-004044.

[24] *Id.*

[25] Lin PC, Lin HJ, Liao YY, Guo HR, Chen KT, *Acute Poisoning with Neonicotinoid Insecticides: a Case Report and Literature Review*, 112 (4) Basic Clin Pharmacol. Toxicol. 282-6 (Apr. 2013), doi: 10.1111/bcpt.12027, https://bit.ly/3b5IGIE; Phua DH, Lin CC, Wu ML, Deng JF, Yang CC, *Neonicotinoid Insecticides: An Emerging Cause of Acute Pesticide Poisoning*, 47 (4) Clin. Toxicol. (Phila) 336-41 (Apr. 2009), doi: 10.1080/15563650802644533, https://bit.ly/35us461; Imamura T, Yanagawa Y, Nishikawa K, Matsumoto N, Sakamoto T, *Two Cases of Acute Poisoning with Acetamiprid in Humans*, 48 (8) Clin. Toxicol. (Phila) 851-3 (Oct. 2010), doi: 10.3109/15563650.2010.517207, https://bit.ly/2W0dQqr; Wang X, Anadón A, Wu Q, Qiao F, Ares I, Martínez-Larrañaga MR, Yuan Z, Martínez MA, *Mechanism of Neonicotinoid Toxicity: Impact on Oxidative Stress and Metabolism*, 58 Ann. Rev. Pharmacol. Toxicol. 471-507 (Jan. 6, 2018), doi:10.1146/annurev-pharmtox-010617-052429, https://bit.ly/2YEE5US.

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an alarming poisoning report; symptoms lasting well over a month would surely have impaired this person's ability to conduct normal daily activities or return to work, and swelling that restricted the neck enough to alter his voice must have posed at least some threat to his breathing.

On the whole, these human poisoning reports make clear the following points: neonic poisoning elicits neurological symptoms; poisoning by neonics and organophosphates elicit the same symptoms; people are being poisoned by neonics in the course of ordinary usage of products available over the counter; and, unlike for organophosphates, there is no antidote for neonic poisoning.

iii. Neurotoxic effects may be much more severe when exposures take place during critical windows of development

As discussed in detail above, there is general scientific consensus that the developing brain is particularly vulnerable to toxic chemical exposures during critical windows of vulnerability during embryonic and fetal development, infancy, and early childhood. A published consensus statement by scientists, health professionals and clinicians, and professional societies wrote: "During these windows of development, toxic chemical exposures may cause lasting harm to the brain that interferes with a child's ability to reach his or her full potential."[26] This esteemed collection of authors specifically identified neonic pesticides as a regrettable substitute for the organophosphate pesticides, given that neonics share a similar mechanism of toxicity (AChR agonists) and signs and symptoms of poisoning with the OP pesticides.

A recent systematic review of publicly-available literature on unintentional human exposures to neonics (such as from agricultural uses or consumer products) reported a link between those exposures and elevated risk of developmental or neurological damage. Effects linked to neonic exposures include malformations of the developing heart and brain and a cluster of symptoms including memory loss and finger tremors.[27]

- In a study of 407 children in the U.S. with confirmed autism spectrum disorder (ASD), researchers found a statistically significant association between prenatal exposure to imidacloprid and ASD in study participants who self-identified as "frequent users" of flea and tick medicines containing imidacloprid (OR=2.0, 95% CrI: 1.0, 3.9).[28]

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[26] Bennett et al., TENDR Consensus Statement (2016), doi: 10.1289/EHP358. PMID: 27479987; PMCID: PMC4937840, https://bit.ly/3dcKvyl.

[27] Cimino AM, Boyles AL, Thayer KA, Perry MJ, *Effects of Neonicotinoid Pesticide Exposure on Human Health: A Systematic Review*, 125 (2) Env. Health Perspectives 155-62 (Feb. 2017), doi: 10.1289/EHP515, https://bit.ly/3dejHOz.

[28] Keil A, Daniels J, Hertz-Picciotto I, *Autism Spectrum Disorder, Flea and Tick Medication, and Adjustments for Exposure Misclassification: The CHARGE (Childhood Autism Risks from Genetics and Environment) Case-Control Study*, 13 (1) Environ. Health 3 (2014), https://bit.ly/2yd5Fy4.

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- In a study of 101 children in the U.S. with confirmed heart defects, researchers found a statistically significant association between residential proximity to agricultural use of imidacloprid and heart defects (tetralogy of Fallot) (AOR 2.4, 95% CI: 1.1, 5.4).[29]
- In a study of 73 babies born with anencephaly (absence of large portion of the brain, usually resulting in stillbirth), researchers reported a 'suggestive association' between residential proximity to agricultural use of imidacloprid and anencephaly (AOR 2.9, 95% CI: 1.0, 8.2).[30]
- In a study of 35 people in Japan that reported symptoms, researchers found a statistically significant association between acetamiprid exposure (urinary DMAP) and increased prevalence of memory loss, finger tremor, and other symptoms of unknown origin (OR 14, 95% CI: 3.5, 57).[31]

While the studies to date have limitations, the authors warn that, "[g]iven the widespread use of neonicotinoids in agriculture and household products and its increasing detection in U.S. food and water, more studies on the human health effects of chronic (non-acute) neonicotinoids exposure are needed."[32]

In fact, there is overwhelming scientific concern expressed that, "[u]nder our current system, when a toxic chemical or category of chemicals is finally removed from the market, chemical manufacturers often substitute similar chemicals that may pose similar concerns or be virtually untested for toxicity. This practice can result in 'regrettable substitution' whereby the cycle of exposures and adverse effects starts all over again."[33] Indeed, this is exactly what has happened—many uses of organophosphate pesticides have been replaced with neonics, a class of pesticides that target the same receptors in the brain and nervous system, to elicit the similar poisoning signs and symptoms.

iv. Societal costs of neurodevelopmental disabilities are substantial

To realistically evaluate the adverse impacts of the neonic pesticides, EPA must consider the risks across the U.S. population; what may seem insignificant on an individual scale can be highly significant when multiplied over 300 million people. For example, it may be difficult to

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[29] Carmichael SL, Yang W, Roberts E, Kegley SE, Padula AM, English PB, Lammer EJ, Shaw GM, *Residential Agricultural Pesticide Exposures and Risk of Selected Congenital Heart Defects Among Offspring in the San Joaquin Valley of California*, 135 Environ. Res. 133-38 (Nov. 2014), https://bit.ly/35sYHkz.

[30] Yang W, Carmichael SL, Roberts EM, Kegley SE, Padula AM, English PB, Shaw GM, *Residential Agricultural Pesticide Exposures and Risk of Neural Tube Defects and Orofacial Clefts Among Offspring in the San Joaquin Valley of California*, 179 (6) Am J Epidemiol. 740-48 (Mar. 15, 2014), https://bit.ly/2ypYoe2.

[31] Marfo JT, Fujioka K, Ikenaka Y, Nakayama SM, Mizukawa H, Aoyama Y, Ishizuka M, Taira K, *Relationship between Urinary N-Desmethyl-Acetamiprid and Typical Symptoms including Neurological Findings: A Prevalence Case-Control Study*, 10 (11) PLoS One. e0142172 (Nov. 4, 2015), https://doi.org/10.1371/journal.pone.0142172.

[32] Cimino et al. (2017), doi: 10.1289/EHP515, https://bit.ly/2zVubE9.

[33] Bennett et al., TENDR Consensus Statement (2016), doi: 10.1289/EHP358. PMID: 27479987; PMCID: PMC4937840, https://bit.ly/2WtGFKX.

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determine the adverse impact of a loss of 5 IQ points in an individual over a lifetime. But, using lead, manganese, and methylmercury poisoning as case studies, experts have calculated that reducing the U.S. national average IQ from 100 to 95, will reduce the number of 'gifted' individuals (IQ over 130) by 3.6 million people (from 6 to 2.4 million people with high IQ), and increase the number of individuals requiring remedial academic support (IQ below 70) by about the same amount (from 6 to 9.4 million people with low IQ).[34] This shift in the population IQ curve comes at a tremendous expense to society, as well as affected individuals, their care-givers and loved ones.

The social costs of neurodevelopmental disabilities have been described by prestigious physicians in a scientific paper published in Lancet Neurology: "Neurodevelopmental disabilities, including autism, attention-deficit hyperactivity disorder, dyslexia, and other cognitive impairments, affect millions of children worldwide, and some diagnoses seem to be increasing in frequency. Industrial chemicals that injure the developing brain are among the known causes for this rise in prevalence… All these disabilities can have severe consequences - they diminish quality of life, reduce academic achievement, and disturb behavior, with profound consequences for the welfare and productivity of entire societies"[35] The contribution of pesticides, and particularly those that impair acetylcholine, are specifically called out by the authors: "Some pesticides inhibit cholinesterase function in the developing brain, thereby affecting the crucial regulatory role of acetylcholine before synapse formation."[36]

In a recent published paper, a team led by physician and policy expert, Dr. Leo Trasande valued the cost to the U.S. economy from neurodevelopmental disabilities due to OPs alone from 2001 to 2008 to be roughly 26.6 million lost IQ points, with an associated economic loss of around $30-50 billion annually.[37] Tragically, these could have been prevented, with more effective regulations, and earlier action by EPA to rein in these brain-toxic insecticides.

The public health benefit of cancelling many OP uses, including the majority of residential uses, was demonstrably effective in reducing harmful OP exposures over the last decade.[38] However, the achievable health benefits are markedly reduced by EPA's continued

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[34] Weiss B, *Lead, Manganese, and Methylmercury as Risk Factors for Neurobehavioral Impairment in Advanced Age*, 2011 Int. J. Alzheimers Dis. 607543 (Dec. 27, 2010), doi: 10.4061/2011/607543, https://bit.ly/2YBKGQ3.

[35] Grandjean & Landrigan (2014), doi: 10.1016/S1474-4422(13)70278-3.3. https://bit.ly/3c3evNp.

[36] *Id.*

[37] Gaylord A, Osborne G, Ghassabian A, Malits J, Attina T, Trasande L, *Trends in Neurodevelopmental Disability Burden Due to Early Life Chemical Exposure in the USA from 2001 to 2016: A Population-Based Disease Burden and Cost Analysis*, 502 Mol. Cell. Endocrinol. 110666 (Feb. 15, 2020), doi: 10.1016/j.mce.2019.110666 (using EPA standard assumptions that each IQ point loss incurs an economic cost of $22,268), https://bit.ly/3fik1gZ.

[38] *Id.*

approval of the neonic replacements, since they are also neurotoxic. Dr. Trasande's recent paper warns of, "the use of potentially harmful substitutions."[39]

The cost of neurodevelopmental disabilities, when multiplied across the U.S. population, results in measurable suffering to individuals, families, communities, and the nation. Some portion of these are the result of exposure to neonics that may seem low or transient, but that occur during critical windows of development and therefore result in lasting harm.

c. EPA's Assessment of Developmental Effects

i. EPA's risk calculation

EPA's determination that a pesticide meets the standards of the FDCA and FIFRA is based on an assessment of the overall risk of potential harm posed by the pesticide, at relevant levels of exposure. To identify "risks of concern" that trigger regulatory action, EPA first identifies a toxicological threshold of concern, called the Point of Departure (POD) usually from a guideline study submitted by the pesticide registrant. According to EPA, "[t]his point can be the lower bound on dose for an estimated incidence or a change in response level from a dose-response model (BMD), or a [no observed adverse effect level (NOAEL)] or [lowest observed adverse effect level (LOAEL)] for an observed incidence, or change in level of response."[40] The POD is used to mark the beginning of an extrapolation to determine risks associated with (usually lower) environmentally relevant human exposures.

Once EPA identifies the POD, it applies uncertainty factors (UFs). Uncertainty factors include: the 10X inter-species UF, used to account for uncertainty about using toxicity in animals as a proxy for toxicity in humans; the 10X intra-species UF to account for variation in susceptibility among people; and the default 10X FQPA factor "to take into account potential pre- and post-natal toxicity and completeness of the data with respect to exposure and toxicity to infants and children." 21 U.S.C. § 346a. In some circumstances, EPA also applies uncertainty factors such as the database uncertainty factor or other factors that account for extrapolation of data from a LOAEL to a NOAEL, or from a subchronic study to a chronic risk estimate.[41]

The acute and chronic reference dose (RfD) is the POD divided by the UFs to provide an added margin of protection, and to account for limitations in the data. The RfD is defined as an estimate (with uncertainty) of a daily oral exposure (for either an acute duration of roughly

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[39] *Id.* (applying EPA standard assumptions that each IQ point loss incurs an economic cost of $22,268).

[40] EPA, Terms and Acronyms, https://bit.ly/2YuN62Z.

[41] EPA also expresses risk in terms of the Level of Concern and Margin of Exposure. EPA determines the Level of Concern, LOC, by multiplying UFs. For example, if EPA applies a 10X UF for interspecies variability (extrapolating from a rodent study to human risk), and another 10X UF for intraspecies variability (differences between individual people across a diverse population), then they are multiplied to produce a total LOC of 100. The Margin of Exposure (MOE) is calculated as the POD divided by the actual or projected environmental exposure of interest. If the MOE is greater than the LOC, then EPA concludes that there are no risks of concern. In this example, all MOE's between 0 and 100 are of concern, and all MOE's over 100 are not of concern.

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twenty-four hours, or a chronic duration up to a lifetime), "to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime."[42] If expected or actual exposure exceeds the RfD, EPA must conclude there is a risk of concern, which necessitates tolerance reductions until the expected exposures once again fall below the threshold level.

ii. EPA must use the most sensitive endpoint in its risk analyses

It is long-standing EPA policy, when assessing developmental effects, that "the most sensitive developmental effect (i.e., the critical effect) from the most appropriate and/or sensitive mammalian species is used for determining the NOAEL, LOAEL, or the benchmark dose."[43] Similarly, EPA's guidance on the process for developing a reference dose/concentration states that it should be based on a, "critical effect," defined as "the first adverse effect, or its known precursor, that occurs to the most sensitive species as the dose rate of an agent increases."[44] Indeed, in the neonic PIDs, EPA explains that the risk assessments purportedly use the "most sensitive endpoint from the respective toxicity databases." *See, e.g.*, Imidacloprid Proposed Interim Determination at 19 (Jan. 2020) (Imid. PID) This endpoint is used for good reason: if the most sensitive endpoint is not used, the resulting risk calculation will fail to protect for crucial developmental effects.

iii. DNT studies are the best indicator of developmental neurotoxicity

The Developmental Neurotoxicity (DNT) guideline was first developed by the EPA as a draft in 1986, as a final guideline in 1991, and updated with minor modifications in 1998.[45] A version developed by the Organization for Economic Cooperation and Development (OECD), Test Guideline (TG) 426, was published in 1995 and finalized in 2007.[46] It was developed in response to decades of scientific evidence of "the potential for physical, pharmaceutical, and environmental agents to affect the development and function of the nervous system after prenatal and early post-natal exposure" in ways that were not adequately captured in existing tests for prenatal developmental toxicity, reproductive toxicity, and multi-generational toxicity. Most notably, the DNT test guideline addresses the fact that the toxic chemical exposures to the brain and nervous system during critical windows of development may lead to abnormal behavioral and functional impairments, motor and sensory functions, and learning and memory deficits that are not reliably detected in other guideline toxicity tests. A published review of existing

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[42] EPA website of Terms and Acronyms, https://bit.ly/2YuN62Z.

[43] EPA, Guidelines for Developmental Toxicity Risk Assessment. U.S. Environmental Protection Agency, Risk Assessment Forum, Washington, DC, (1991), https://bit.ly/3aSeKJO.

[44] EPA, A Review of the Reference Dose and Reference Concentration Processes at G-2 (Dec. 2002), https://bit.ly/2zUF1KL.

[45] EPA, Health Effects Guidelines: OPPTS 870.6300 Developmental Neurotoxicity Study (1998), https://bit.ly/3c1esl7.

[46] OECD, Test Guideline 426: Developmental Neurotoxicity Study (2007), https://bit.ly/2YtYpZI.

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guideline tests by authors that include scientists from EPA, Bayer CropScience (the main registrant for neonics), Syngenta, and OECD reaffirmed the value of the DNT for use in chemical evaluation and risk assessment, and that its absence should trigger the use of additional uncertainty factors:

> The OECD DNT TG 426 (OECD 2007) represents the best available science for assessing the potential for DNT in human health risk assessment, and data generated by DNT studies are relevant and reliable for this assessment. The test methods used in the DNT have been subjected to an extensive history of international validation, peer review, and evaluation that is contained in the public record. The reproducibility, reliability, and sensitivity of these methods have been demonstrated, using a wide variety of test substances. Multiple, independent, expert scientific peer reviews affirm these conclusions, as described in this document. The OECD DNT TG 426 provides an outline of behavioral domains and morphologic end points, relevant to human neurodevelopment, that should be examined to assess potential DNT of a test compound. The results from DNT studies are used for hazard/risk assessment purposes, and in cases where data from a DNT study are not available, additional uncertainty factors may be employed by regulators to address the need for DNT data from a regulatory standpoint.[47]

In sum, DNT studies represent the "gold standard" for identifying developmental neurotoxic effects. To establish a tolerance for neonics, therefore, the DNT studies must support EPA's determination that neonics are reasonably certain to cause no harm. 21 U.S.C. § 346a(b)(2)(A)(ii).

III. EPA DISREGARDS EVIDENCE OF LOW-DOSE HARM, DERIVES INSUFFICIENTLY PROTECTIVE RFDs FOR IMIDACLOPRID, THIAMETHOXAM, AND ACETAMIPRID

EPA's reference dose (RfD) calculations for imidacloprid, thiamethoxam, and acetamiprid are not sufficiently protective and result in tolerances for these chemicals that are not "safe," in violation of the FDCA, 21 U.S.C. § 346a(B)(2)(A)(i). In each case, EPA ignores statistically significant effects at mid-and low-dose groups in the registrant-submitted DNT studies, meaning it fails to use the most sensitive endpoint in accordance with EPA guidance and practice. *See* Section II(c)(2). Moreover, EPA fails to apply factors that are typically used to

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[47] Makris SL, Raffaele K, Allen S, Bowers WJ, Hass U, Alleva E, Calamandrei G, Sheets L, Amcoff P, Delrue N, Crofton KM, *A Retrospective Performance Assessment of the Developmental Neurotoxicity Study in Support of OECD Test Guideline 426*, 117 (1) Environ. Health Perspect. 17-25 (Jan. 2009), doi: 10.1289/ehp.11447, https://bit.ly/2WpqXAp.

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account for uncertainty in its calculation of the RfD and, in the case of imidacloprid, ignores a more sensitive endpoint—thyroid toxicity.

a. Imidacloprid

EPA's current acute and chronic RfD are both based on the same study, a subchronic oral study in dogs reporting on increased incidence of tremors (NOAEL/LOAEL of 8 and 22 mg/kg respectively). EPA, Imidacloprid. Acute and Chronic Aggregate Dietary (Food and Drinking Water) Exposure and Risk Assessments for the Registration Review Risk Assessment at p. 9, Table 3 (Jun. 2017), EPA-HQ-OPP-2008-0844-1236 ("Imid. Dietary RA"). For each, EPA applied a 100X factor (10X animal-to-human, and 10X inter-human variability, FQPA 1X), resulting in the same acute and chronic PAD, 0.08 mg/kg-day. Independently of EPA's unlawful failure to apply the 10X FQPA factor, *see infra* Section III, this value is insufficiently protective and results in imidacloprid tolerances that are not "safe," in violation of the FDCA. 21 U.S.C. § 346a(b)(2)(A)(i).

Initially, EPA fails to explain why the NOAEL of 8 mg/kg is the appropriate endpoint, when its previous RfD—based on thyroid toxicity in a combined chronic toxicity/ carcinogenicity rat study—reported a NOAEL of 5.7 mg/kg.[48] This failure to use thyroid toxicity, the more sensitive endpoint, in its risk calculations is arbitrary and capricious.

Moreover, EPA arbitrarily disregards statistically significant effects at low- and mid-doses in the rat DNT study submitted by Bayer ("Imid. Rat DNT Study") to fulfill DNT Guidelines from the OECD (TG 426) and EPA (OPPTS 870.6300).[49] Female offspring at the lowest dose (8 mg/kg-day) had a statistically significant elevated auditory startle reflex peak amplitude for all subjects at post-natal day 60.[50] EPA reviewers noted that peak amplitude was also increased for the mid-dose females (20 mg/kg-day), and high-dose females (55-58 mg/kg-day), but did not reach statistical significance. EPA reviewers considered the significant effects in the low-dose group "spurious" because there was no dose-relationship and the high-dose group was elevated but more similar to control group values. However, this isn't accurate. There was in fact a dose-relationship; the effect was most severe at the lower dose and decreased with increasing doses. There are many reasons why this may be so, the most obvious one is that the higher doses were associated with more toxicity, possibly even cell death, overwhelming the behavioral response. In any case, evidence of harm should not be dismissed, particularly when it is statistically significant, relevant to health and welfare, and detected in a test that is specifically designed to detect these effects.

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[48] EPA, Imidacloprid - Report of the Hazard Identification Assessment Review Committee (Oct. 31, 2002) (describing the basis for the Acute RfD (Acute neurotoxicity study - rat. MRID 43170301) and the Chronic RfD (Combined chronic toxicity/carcinogenicity - rat. MRID 42256331)).

[49] Sheets, LP, *A Developmental Neurotoxicity Screening Study with Technical Grade Imidacloprid in Wistar Rats*, Bayer Corporation, MRID 45537501 (Sept. 14, 2001). Unpublished.

[50] *See* Imid. Rat DNT Study at Table 10.

In the same rat DNT study, EPA also failed to secure additional data to characterize brain morphological effects detected in high-dose animals.[51] EPA reviewers noted reduced thickness of the caudate/putamen area of the brain in high dose animals, but Bayer had failed to include data for the low and mid dose groups for this endpoint.[52] As a result, EPA classified the study as "acceptable/non-guideline" and said it could be upgraded upon submission of additional analytical data of the brain sections at intermediate doses.[53] If the updated data were submitted—which does not appear to have happened—they were never made public or integrated into EPA's analysis. In the absence of this information, the presumption should be that there may be brain morphological effects in the low- and mid- dose groups.

Instead, EPA reviewers concluded that the mid-dose (20 mg/kg-day) was a NOAEL for both dams and offspring, based on decreased food consumption in dams and decreased body weight and activity in offspring at the high dose. This fails to account for potential low and mid dose effects on the thickness of the caudate/putamen brain regions, and effects on the auditory reflex in offspring at the low-dose. [54]

In an April 2010 Federal Register Notice establishing tolerances for imidacloprid on foods, EPA explained that "in the rat developmental neurotoxicity study, a decrease in the caudate/putamen width was noted in female pups," and "there was evidence of an increased qualitative susceptibility in the rat developmental neurotoxicity study."[55] Later in the notice, however, EPA explains why it dismissed this evidence of developmental sensitivity. EPA claims: (i) that the effects in the pups are well-characterized with a clear NOAEL; (ii) the pups and dams had the same NOAEL; and (iii) the doses and endpoints selected for regulatory purposes will protect against effects in the offspring at the higher doses in the rat DNT study. As explained above, these statements are invalid. The study failed to identify a proper NOAEL for the offspring because there were statistically significant effects at the low dose for auditory reflex and EPA requested, but never received, the low and mid dose data for caudate/putamen width. Had EPA taken into account the low dose auditory reflex effects, the rat DNT study would have failed to identify a NOAEL for offspring. It is, therefore, arbitrary for EPA to conclude that other regulatory endpoints would protect against offspring effects detected in the rat DNT.

Because EPA must use the most sensitive endpoint, *see* Section I(c)(2), it must use the low-dose group in the rat DNT as the point of departure for its risk analysis. Had EPA used the lowest dose in the rat DNT as a point of departure, it would have based its risk calculation on the *LOAEL* of 8 mg/kg. Because the study did not indicate a NOAEL, EPA should apply an

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[51] Cheryl Bast., Data Evaluation Record: Imidacloprid, STUDY TYPE: Developmental Neurotoxicity Study – Rat, MRID 45537501 (Oct. 8, 2002), https://bit.ly/2KX7HEZ.

[52] Imid. Rat DNT Study at Table 15 (morphometric data in offspring).

[53] Bast (2002), https://bit.ly/2KX7HEZ.

[54] *Id.*

[55] 75 Fed. Reg. 22,245, 22,246 (April 28, 2010).

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additional uncertainty factor of 10X to extrapolate from the LOAEL to a NOAEL, in accordance with EPA's standard practice.[56] Had EPA undertaken this proper analysis, it would have calculated an acute RfD (aRfD) of 0.008 mg/kg, 10-fold lower than the current aRFD/chronic RfD (cRfD). Moreover, as explained in Section IV, EPA should have applied the full 10X FQPA child safety factor. Accordingly, EPA's current RfD is 100 times too high, resulting in unsafe tolerances that violate the FDCA.

Even if the endpoint selected by EPA (subchronic dog) is proper—and it is not—the agency failed to apply the uncertainty factor typically applied when extrapolating from a subchronic study to a chronic risk estimate. EPA guidance provides:

> A default value of 10 for this [uncertainty factor] is applied to the NOAEL/LOAEL . . . from the subchronic study on the assumption that effects from a given compound in a subchronic study occur at a 10-fold higher concentration than in a corresponding (but absent) chronic study.[57]

Without explanation, EPA fails to apply this factor for imidacloprid.

EPA's chronic RfD/POD used in the imidacloprid PID is based on a *subchronic* oral study in dogs reporting on increased incidence of tremors (NOAEL/LOAEL 8 and 22 mg/kg respectively.[58] For each, EPA applied two UFs: 10X animal-to-human and 10X inter-human variability, resulting in a chronic RfD of 0.08 mg/kg/day. EPA, therefore, uses a subchronic study to predict a chronic risk estimate. According to EPA's guidance, it should have included an additional UF to account for uncertainty in this prediction, resulting in an RfD of 0.008 mg/kg/day—which is 10 times lower than EPA's current chronic RfD.

Applying this UF is crucial, as subchronic studies may miss more sensitive endpoints, detection of which requires a longer exposure period. For example, EPA had previously used thyroid toxicity—detected in a chronic study—as its critical endpoint for imidacloprid. If EPA relied only on subchronic studies of imidacloprid's toxicity, it would have missed this endpoint entirely.

In sum, EPA's RfD for imidacloprid is too high because it fails to use the most sensitive endpoint. Moreover, had EPA used the most sensitive endpoint—the low dose auditory reflex in rats—it should have applied a 10X uncertainty factor to extrapolate from the LOAEL according to EPA standard practice. Even assuming the subchronic endpoint used by EPA is proper, EPA should have applied an uncertainty factor to account for its reliance on a subchronic study to

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[56] EPA, A Review of the Reference Dose and Reference Concentration Processes (Dec. 2002), https://bit.ly/2zUF1KL. ("Section 4.5.4. LOAEL-to-NOAEL UF: A UF (default 10) is typically applied to the LOAEL when a NOAEL is not available.").

[57] *Id.*

[58] Imid. Dietary RA at 9.

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characterize chronic effects as counseled by EPA guidance. At a minimum, EPA must explain its decisions not to apply these UFs. These shortcomings indicate that EPA's determination that the RfD used is protective of developmental endpoints is arbitrary and unsupported.

b. Thiamethoxam

Syngenta Crop Protection sponsored the rat DNT study of thiamethoxam.[59] It reported on significant effects in the brain morphometric data (reduced size of some areas of the brain in treated offspring). However—as with the imidacloprid DNT study above—this study initially failed to include data for many of the low and mid dose groups. EPA noted, "The original developmental neurotoxicity (DNT) study report only had brain morphometric measurements in low- and mid-dose groups if changes in the high-dose group were statistically significant at the 0.01 level." EPA requested and received data for brain morphometric measurements in the low and mid dose groups when changes in the high dose groups were significant at the 0.05 level, and in any brain sections contiguous to sections with substantial changes. This section discusses EPA's data evaluation record for the updated submission with the additional data (MRID 47034201), hereafter the "Thiam. DNT Review."[60]

EPA classified the study as Acceptable/Non-Guideline for DNT, saying that it could be used for regulatory purposes, but that EPA was awaiting additional review of the positive control data. EPA and Syngenta had concerns with the control data because brain regions seemed to be larger than historical control data that Syngenta provided with the additional brain morphometric measurements. *See* Thiam. DNT Review at 33-37. Initially, however, no rationale was provided for why the within-experiment (concurrent) controls should not be used. Unless there is a very serious reason to disregard those data, EPA policy and scientific best practice is always to use the within-experiment control data.[61] This is because the concurrent control animals were subjected to the exact same circumstances as the treated animals, with the only difference being the treatment, whereas historical controls may have had different bedding, housing conditions, feed, interactions with handlers, number of animals per cage, or myriad other factors that can impact growth, development, and survival. As neither Syngenta nor EPA has presented any reason why the concurrent controls are inappropriate, their exclusion is arbitrary.

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[59] Brammer A, Thiamethoxam: Developmental Neurotoxicity Study in Rats, MRID 46028202 (May 29, 2003), Unpublished; Brammer A, Thiamethoxam: Preliminary Developmental Neurotoxicity Study in Rats, MRID 46028201 (May 22, 2003), Unpublished; Brammer A, Thiamethoxam: Supplement to Developmental Neurotoxicity Study in Rats: (Supplemental to MRID Number 46028202), MRID 47034201 (2007).

[60] EPA, THIAMETHOXAM. Review of Developmental Neurotoxicity Study including Brain Morphometry Data in Low- and Mid-Dose Groups, MRID 46028202 main study, 47034201 additional morphometry (March 9, 2007) ("Thiam. DNT Review"). NRDC cites a version of the Thiam. DNT Review (Attachment A) received via a FOIA request to the agency; the previous publicly available version was illegible in certain areas.

[61] EPA, Guidelines for Carcinogen Risk Assessment. EPA/630/P-03/001F. Section 2.2.2.1.3 Concurrent and historical controls (Mar. 2005), https://bit.ly/3fiNJTo.

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In the thiamethoxam DNT study, the offspring demonstrated several adverse effects at the low (4.3 mg/kg) and mid-doses (34.5 mg/kg) at which the adult mother did not show effects; these included a thinner brain cortex, altered auditory startle reflexes, delayed reproductive development (delayed preputial separation) in males, and an increase in stillbirths.[62] These effects in offspring were statistically significant in many of the low and mid dose groups, and all the high dose (298.7 mg/kg) groups.

It is particularly relevant that the cortex, thalamus, and cerebellum were heavily affected brain regions, given that they are all areas known to be heavily populated with nAChRs that contain the α4β2 subunit,[63] the target of neonics. This further confirms that the observed effects are related to exposure to thiamethoxam, through its established mechanism of toxicity.

Despite significant adverse effects in all dose groups, EPA disregarded the low and mid-dose group effects, stating: "The brain morphometric changes in low- and mid-dose groups were not considered treatment related because statistically significant differences between concurrent controls and low- and mid-dose groups were sporadic and did not show consistent dose-response relationship. In addition, concurrent controls for most brain regions were on the high end of the historical control values and in some cases exceeded them." Thiam. DNT Review at 30). This position controverts established EPA guidance, which is clear that a consistent dose-response relationship is not necessary to establish causality. [64] Moreover, concurrent control data is the appropriate comparison group, not historical control data, unless there is a valid scientific reason to believe that the control data are flawed in some way—EPA, to the contrary, presents no reasoning at all.[65]

Ultimately, EPA calculated the following acute and chronic points of departure for its risk analysis in the PIDs:[66]

- Acute RfD of 0.35 mg/kg (based on a NOAEL of 34.5 mg/kg in the rat DNT study for decreased body weight and reduced brain morphometric measurements, and a total uncertainty factor of 100).
- Chronic RfD of 0.012 mg/kg (based on a NOAEL of 1.2 mg/kg testes abnormalities in the rat two-generation reproduction study, and a total uncertainty factor of 100).

In failing to use the lowest dose as the point of departure, EPA failed to adhere to its own guidelines to use the most sensitive endpoint in its risk assessments. EPA must use the lowest

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[62] EPA, Thiam. DNT Review (2007).

[63] Posadas et al. (2013), doi: 10.2174/1570159X11311030005, https://bit.ly/35wTg47.

[64] EPA, Guidelines for Carcinogen Risk Assessment, EPA/630/P-03/001F at 41 (Mar. 2005), https://bit.ly/3fiNJTo.

[65] *Id.*

[66] EPA, Thiamethoxam Draft Human Health Risk Assessment for Registration Review (2017) ("Thiamethoxam Health RA").

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dose to calculate the acute RfD, and since it is a LOAEL, an additional uncertainty factor of 10X should be added.[67]

Had EPA used the lowest dose in the DNT study as a point of departure (4.3 mg/kg) and a 10X uncertainty factor to account for the lack of NOAEL, it would have calculated an aRfD of 0.0043 mg/kg (LOAEL of 4.3 mg/kg, and UFs of 10X interspecies, 10X intraspecies, 10X LOAEL-to-NOAEL). This makes EPA's aRfD 81 times too high and, therefore, not protective of developmental effects. Moreover, as explained in Section III, had EPA retained the legally required 10X FQPA safety factor, the aPAD would be 0.00043 mg/kg, or 810 times too high to protect against developmental harm.

c. Acetamiprid

In 2001, EPA identified the need for a DNT study for acetamiprid based on several factors.[68] First, in the two-generation reproduction study, increased quantitative susceptibility was observed in rat pups and a delay in age to attain preputial separation was observed at a dose level where no parental toxicity was observed. Second, in the acute neurotoxicity study, clinical signs of neurotoxicity were observed on the day of dosing. Third, in the subchronic feeding study in the mouse, a decrease in mean absolute brain weight was observed in females.

The sponsor, Nippon Soda Co, submitted a DNT study dated 2003 (MRID 46255619) ("Acet. DNT Study").[69] EPA reviewed it and classified it as acceptable/non-guideline, saying that it may be used for regulatory purposes, but that it did not satisfy the DNT guideline "due to the inadequacies in the assessment of motor activity and learning and memory in the offspring, and pending the evaluation [sic] the submitted positive control data."[70] EPA states that, "No conclusions can be made on the effects of acetamiprid on learning and memory because of the high variability in the data."[71]

Despite the high variability across the data, making it difficult to detect treatment-related effects (bias towards the null), the EPA HED review concluded that there was no maternal effects (NOAEL at high dose, 45 mg/kg/day) and the offspring LOAEL was the mid dose of 10 mg/kg/day (the offspring NOAEL was the low dose of 2.5 mg/kg/day) based on a decreased

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[67] EPA, A Review of the Reference Dose and Reference Concentration Processes (Dec. 2002), https://bit.ly/2zUF1KL ("Section 4.5.4. LOAEL-to-NOAEL UF: A UF (default 10) is typically applied to the LOAEL when a NOAEL is not available.").

[68] EPA, HIARC Meeting on Acetamiprid, Briefing Package (Sept. 20, 2001).

[69] Nemec M, An Oral Developmental Neurotoxicity Study in Rats, MRID 46255619 (Nov. 21, 2003), Unpublished.

[70] EPA, Data Evaluation Record, Acetamiprid. Study types: Developmental Neurotoxicity – Rat, MRID 46255619 (Feb. 28, 2008), https://bit.ly/35rhFrB.

[71] EPA, Memo. ACETAMIPRID DNT STUDY (WIL-21193): Statistical Analyses for Auditory Startle Response (July 24, 2007) (Attached at p. 40 to the Data Evaluation Record, Acetamiprid Developmental neurotoxicity - rat. MRID 46255619).

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maximum auditory startle response in males on post-natal day (PND) 20 and PND 60. The registrant opposed this conclusion, arguing that the mid-dose effects was a NOAEL.

Following the release of the DNT Workgroup's conclusion, the registrant submitted a new statistical analysis conducted by Exponent, Inc. (MRID 47181101) using the same data, confirming the registrant's initial conclusions that there were no significant effects at the mid-dose. Acet. DNT study at 42.

However, the EPA Chemistry and Exposure Branch (CEB) disagreed with statistical aspects of the Exponent analysis, and instead performed a corrected analysis. The CEB analysis, "using a more appropriate model for data structure and appropriate statistical methods" concluded the auditory startle reflex in male rats was statistically significant at both the mid (10 mg/kg) and high dose (45 mg/kg) compared with control animals (p-value=0.0015). Acet. DNT study at 46.[72]

Nonetheless, in the December 2017 Acetamiprid Draft Human Health Risk Assessment ("Acet. Health RA") for registration review, EPA reversed the conclusions of its own scientists with no explanation, and adopted the registrant/Exponent conclusions, calling the mid dose the NOAEL (10 mg/kg), and the high dose the LOAEL (45 mg/kg), based on "… decreased maximum auditory startle response in males on PND 20/60 in the offspring." Acet. Health RA at 21; 78, Table A.2. Because EPA disregarded HED's conclusions that there were significant adverse effects in offspring at the mid dose (10 mg/kg), EPA's current assessment concludes that the offspring and dams share the same NOAEL (10 mg/kg) and LOAEL (45 mg/kg), thus denying the evidence of increased sensitivity in the juvenile animals. In summary, EPA has disregarded its own scientific opinions from two separate internal branches in favor of a problematic and inappropriate statistical analysis sponsored by the registrant.

EPA should reverse this indefensible position, and instead heed the recommendations of its own experts, to conclude that the DNT study offspring NOAEL is the low dose (2.5 mg/kg). EPA's current chronic dietary RfD/PAD is 0.071, based on the chronic toxicity/carcinogenicity study in rats (NOAEL 7.1 mg/kg, LOAEL 17.5 mg/kg). Had EPA based it on the more sensitive offspring NOAEL from the DNT study, the PAD would be 0.0025 mg/kg (NOAEL 2.5 mg/kg, LOAEL 10 mg/kg, 10Xinterspecies, 10X intraspecies, 1X FQPA). This RfD is almost 30 times more protective than EPA's current calculation.

IV. EPA UNLAWFULLY FAILS TO RETAIN THE DEFAULT FQPA 10X SAFETY FACTOR FOR ALL NEONICS

EPA must retain the full 10X FQPA safety factor ("child safety factor") for each of the five registered neonics. Congress required that the child safety factor "shall be applied" to "take into account" two things: (1) "potential pre- and post-natal toxicity" and (2) "completeness of the data" with respect to exposure and toxicity to infants and children. 21 U.S.C.

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[72] EPA, HIARC Meeting on Acetamiprid, Briefing Package (Sept. 20, 2001).

§ 346a(b)(2)(C)(ii)(II). EPA may only reduce this safety factor if it has "reliable data," *id.*, demonstrating to a "reasonable certainty that no harm will result" to infants and children from the lower margin, *id.* § 346a(b)(2)(A)(ii).

EPA has no such data. Initially, it lacks studies and data needed to fully characterize developmental toxicity to infants and children. Second, EPA has failed to collect registrant-submitted DNT studies for all neonics; where DNT studies are available, they fail to identify a proper NOAEL, fail to include all required data, or both. EPA has, therefore, failed to demonstrate that waiver of the child safety factor is "safe." Accordingly, EPA's tolerance determinations and PIDs are contrary to law and unsupported by substantial evidence.

a. EPA Has Failed to Fully Characterize the Developmental Effects of Demonstrated Thyroid Toxicity

To depart from the legally-required child safety factor, EPA must demonstrate using "reliable data" that a different margin of safety is "safe," meaning there is a reasonable certainty of no harm. 21 U.S.C. § 346a(b)(2)(C)(ii). EPA lacks this data with respect to thyroid toxicity and the impacts of neonic-induced thyroid toxicity on the developing nervous system.

To the contrary, compelling evidence links early-life neonic exposures to adverse thyroid effects, as evidenced in the comments of the Endocrine Society, an international professional society of over 18,000 medical clinicians and science researchers across the globe with expertise in the diseases, disorders, and vulnerabilities of the human hormone system. The Endocrine Society submitted expert comments to all four neonic dockets for this comment period, noting that the impacts of neonicotinoid pesticides on the developing thyroid gland are of great concern. (Attachment B). The Society's comments list a "substantial and increasing body of literature" linking neonicotinoid pesticides to developmental thyroid toxicity, including in wildlife, and in studies that form the basis of EPA's assessments. Moreover, the Endocrine Society warns that there may be no safe level for exposure to chemicals like neonics that disrupt thyroid activity during development. "Consistent with current scientific understanding of the properties of hormones and the endocrine system, these chemicals may have effects at extremely low doses and display non-monotonic dose-responses (NMDR). Consequently, there may in fact be no 'safe' level for these chemicals".

EPA's current risk estimates, which presume a threshold or 'safe level' of exposure, will not provide adequate protection against the risk of harm from even small or transient disruptions to thyroid hormones during critical windows of vulnerability. Accordingly, EPA has failed to support its determination that a lower uncertainty factor will provide the legally required margin of safety—especially for the most sensitive identifiable population, children born to mothers with hypothyroidism.

i. Neonics impair thyroid function

There is a considerable body of scientific evidence demonstrating that neonic pesticides are thyroid-toxic. EPA acknowledges this when selecting thyroid toxicity in industry-sponsored rodent guideline studies for its risk estimates:

- For imidacloprid, regulatory agencies including EPA selected thyroid toxicity in a rat study as the critical endpoint for the chronic RfD (NOAEL of 5.7 mg/kg) for imidacloprid.[73]
- For thiacloprid, regulatory agencies including EPA based its risk estimates for the chronic RfD, incident oral exposures, and all dermal exposures on liver and thyroid toxicity in a combined chronic/carcinogenicity feeding study in rats at 2.5 mg/kg (NOAEL 1.2 mg/kg). EPA notes that the thyroid is affected in rats at lower doses than the liver (Section 3.1). EPA notes that thyroid toxicity is demonstrated in the thiacloprid rodent reproductive studies and subchronic inhalation study.[74]
- Thiacloprid is classified by EPA as "likely to be carcinogenic in humans" based on thyroid and uterine tumors in rats, and ovarian tumors in mice. [75]
- Thiamethoxam induced thyroid and liver toxicity in the dog sub-chronic (28 day) oral toxicity study (MRID 44703324); this study was the basis for EPA's incident oral and inhalation exposure risk estimates (NOAEL of 31.6 mg/kg, LOAEL of 43 mg/kg).[76]

Thyroid toxicity has also been reported in various wildlife exposed under controlled conditions to field-relevant oral doses of neonic pesticides:

- A recent study of white-tailed deer experimentally exposed to environmentally-relevant levels of imidacloprid in their water (0, 1.5, 3.0, 15 micrograms/L) exhibited hypothyroidism and lethargy, as well as decreased body and organ weight, decreased jawbone length, and higher mortality rates for fawns.[77] All these effects are known to be potential results of congenital hypothyroidism.
- A laboratory study of lizards exposed to neonics reported thyroid disruptions with imidacloprid, thiamethoxam, and dinotefuran. The lizards were exposed by oral gavage to 20 mg/kg of the appropriate neonic, once every 3 days for 28 days. Treatments varied regarding whether thyroid activity was increased (thiamethoxam) or decreased (dinotefuran, imidacloprid) compared with control animals.[78]

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[73] EPA, Imidacloprid - Report of the Hazard Identification Assessment Review Committee (Oct. 31, 2002) (describing the basis for the Acute RfD (Acute neurotoxicity study - rat. MRID 43170301) and the Chronic RfD (Combined chronic toxicity/carcinogenicity - rat. MRID 42256331)).

[74] EPA, Thiacloprid in/on Pome Fruits and Cotton. Health Effects Division (HED) Risk Assessment. (July 23, 2003), https://bit.ly/35tOGmY.

[75] *Id.*

[76] Thiamethoxam Health RA.

[77] Berheim et al. (2019), doi: 10.1038/s41598-019-40994-9, https://go.nature.com/2Q1I9Zf.

[78] Wang et al. (2020), doi: 10.1016/j.envpol.2019.113731, https://bit.ly/2W3pP6H.

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- A laboratory study of the Red Munia, a wild bird of India, reported that exposure to imidacloprid through feed for 30 days at 0.5% LD50 reduced thyroid activity.[79]

In summary, EPA and scientific experts agree that the neonic pesticides cause significant impairment to thyroid function, which can lead to various adverse outcomes relevant to human health and environmental risk assessments.

For this reason, the Endocrine Society urges caution regarding the impacts of neonic thyroid toxicity on development. At over 100 years old, the Endocrine Society is the world's oldest, largest, and continuously active society of experts dedicated to understanding, treating, and preventing hormone-related health harms. It has hosted an Annual Meeting of endocrine experts since its inception. The Society also hosts four scientific journals, all of which are highly-ranked and carried by the U.S. National Library of Medicine.[80] In fact, in 2018 the Endocrine Society ranked fifth among publishers in the field of endocrinology and metabolism, and two of its journals ranked in the top 25 out of 145 journals on endocrinology and metabolism.[81] In short, the Endocrine Society is the globally recognized professional society for experts in the science and medicine of hormones. The fact that the Society found the evidence of thyroid toxicity of neonic pesticides compelling enough to submit comments warning EPA to take further action should be considered by EPA as an authoritative expert statement of how serious these potential risks may be.

ii. Healthy thyroid function is critical for normal brain structure and function

The thyroid gland is located within the neck and produces a hormone that is necessary for regulation of many body functions throughout adult life, including heart rate, metabolism, energy, mood, cognitive function, and growth and development. However, early development of the brain and nervous system is especially dependent on healthy thyroid activity. Having a continuous supply of the correct levels of thyroid hormone—not too low or too high—during prenatal brain development is necessary for correct migration of cortical neurons during brain formation (first trimester), neuronal proliferation during cerebellar formation (second trimester), microtubule formation, and myelin deposition (postnatal).[82]

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[79] Pandey & Mohanty (2015), doi: 10.1016/j.chemosphere.2014.11.061, https://bit.ly/2L0ZUWJ.

[80] Endocrine Society Journals are: Endocrine Reviews; The Journal of Clinical Endocrinology & Metabolism; Endocrinology and Metabolism; and, Molecular Endocrinology.

[81] Journal ranking is done by an independent body, in a measurement called the 'Journal Impact Factor, based on the number of times the articles published in that journal are referenced in other published articles, which is an indication of the impact the research is having on the field. See here for Endocrine Society Journals and rankings: https://bit.ly/3fmvTP0.

[82] Glinoer D, *Potential Consequences of Maternal Hypothyroidism on the Offspring: Evidence and Implications*, 55 Horm. Res. 109-114 (2001), https://bit.ly/2SAiZDg.

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Babies born to mothers with low thyroid hormone during pregnancy are at higher risk of neurological deficits including mental retardation.[83] This is because during the first trimester the fetus is completely dependent on thyroid hormone derived from the mother's circulation, and only begins to synthesize its own thyroid hormone within the second trimester (about 20 weeks gestation).[84] While the proportion of maternal and fetal-derived thyroid hormone changes as development progresses, some dependence on maternal hormone continues throughout *in utero* development. For this reason, pregnant women with untreated hypothyroidism during pregnancy are at risk of giving birth to an infant with measurable deficits in IQ, even in cases where the infant is able to produce normal levels of thyroid hormone after birth.[85] Similarly, administration of iodine, a necessary component of thyroid hormone, to iodine-deficient women during the first trimester of pregnancy has been demonstrated to eliminate the incidence of cretinism (severe mental retardation), whereas when similar treatment is administered later in pregnancy it does not provide complete protection for the developing fetus.[86] These data demonstrate the necessity of appropriate thyroid hormone levels during prenatal development, for appropriate brain formation and function.

After birth, the newborn no longer has access to maternal thyroid hormone, and is suddenly and completely dependent on its own thyroid hormone production. These newborns have only enough thyroid iodide stores to last for one day and are therefore reliant on continuous ability to produce the daily requirements for adequate levels of thyroid hormones to support normal brain development. This represents a critical window of development, when even short or transient exposure to thyroid-toxic chemicals can result in adverse neurological effects.

The clinical effects of hypothyroidism, a condition where the thyroid does not produce adequate levels of thyroid hormone, varies according to whether the mother, fetus, or both have hypothyroidism, and how long it persists. In pre-term and newborns with congenital hypothyroidism, researchers have recorded lasting effects in selective memory and attention

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[83] Bernal J, *Thyroid Hormone Receptors in Brain Development and Function*, 3 Nat. Rev. Endocrinol. 249–259 (2007), https://bit.ly/3ddYlRs.

[84] Lafranchi SH, Haddow JE, Hollowell JG, *Is Thyroid Inadequacy During Gestation a Risk Factor for Adverse Pregnancy and Developmental Outcomes?*, 15 (1) Thyroid. 60-71 (2005), https://bit.ly/2z6RlH8.

[85] Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, O'Heir CE, Mitchell ML, Hermos RJ, Waisbren SE, Faix JD, Klein RZ, *Maternal Thyroid Deficiency During Pregnancy and Subsequent Neuropsychological Development of the Child*, 341 (8) N Engl J Med. 549-55 (Aug. 19, 1999), https://bit.ly/2xtjjwn; Pop VJ, Kuijpens JL, van Baar AL, Verkerk G, van Son MM, de Vijlder JJ, Vulsma T, Wiersinga WM, Drexhage HA, Vader HL, *Low Maternal Free Thyroxine Concentrations During Early Pregnancy Are Associated with Impaired Psychomotor Development in Infancy*, 50 (2) Clin. Endocrinol. (Oxf) 149-55 (Feb. 1999), 10.1046/j.1365-2265.1999.00639.x.

[86] Ren Q, Gr D, Cao X, Wang S, Jiang X, Jiang J, Ma E, O'Donnell K, *Effect of environmental supplementation of iodine on infant mortality and growth in children in Xinjiang, China*, 23 (3) Zhonghua Liu Xing Bing Xue Za Zhi 198-202 (Jun. 2002), https://bit.ly/2KYBBJ5.

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deficits, language, hearing, and vestibular function.[87] Congenital hypothyroidism in infants is not uncommon, occurring in one out of every 3,500-5,000 children in North America. Surveys in pregnant women in the U.S. have reported that 2.5% of pregnant women have borderline or subclinical hypothyroidism (TSH concentrations above 6 mU/l), and about 1% are estimated to have frank hypothyroidism. Since there are around 3.7 million babies born annually in the U.S., this represents just under 40,000 infants born to mothers with clinical hypothyroidism. A 1999 study by Dr. James Haddow, medical director, Foundation for Blood Research, showed that children born to mothers with untreated hypothyroidism during pregnancy score lower on IQ tests than children of healthy mothers.[88] Of the 62 women in Dr. Haddow's study, only 14 were diagnosed and receiving treatment for hypothyroidism before their pregnancies. Of those with untreated hypothyroidism, their children's IQ scores averaged 7 points below the children of mother's with normal thyroid hormone levels, and 19% had IQ scores below 85. Children who have an I.Q. less than 85 are more likely to have difficulties in school and may be less successful in their careers and interpersonal relationships. In a subsequent study, researchers reported that pregnant women with borderline or more severe hypothyroidism (TSH levels 6mU/L or greater) have an almost four-times greater risk for miscarriage during the second trimester.[89] This study suggests that 6 out of every 100 late term miscarriages may be attributable to thyroid deficiency during pregnancy.

EPA has not analyzed the impact of neonic thyroid-toxicity on adverse health outcomes associated with hypothyroidism. As there is ample evidence supporting this adverse effect from prenatal neonic exposure, EPA's failure to fully characterize these effects is arbitrary and renders its reduced margin of safety unlawful.

iii. Pregnant women and infants with hypothyroidism are an especially sensitive population

EPA must not only consider thyroid toxicity and its effects on neurodevelopment for the population at large, but it must also consider the "variability of the sensitivities of major identifiable subgroups of consumers." 21 U.S.C. § 346a(b)(2)(D)(vii). Pregnant women and infants with hypothyroidism are one such subgroup that is particularly susceptible to effects of thyroid toxicity.

Because neonic pesticides are thyroid-toxic, they may trigger hypothyroidism in a person who is borderline low thyroid, or worsen it in someone that is already clinically hypothyroidic. Additionally, neonic pesticides may undermine the effects of treatment medications. EPA has not considered any of these possible impacts of neonic exposures on hypothyroidic individuals, and

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[87] Rovet JF, *Congenital Hypothyroidism: an Analysis of Persisting Deficits and Associated Factors*, 8 (3) Child Neuropsychol. 150-62 (Sep. 2002), https://bit.ly/2WFB8kH.

[88] Haddow et al. (1999), https://bit.ly/2xtjjwn.

[89] Allan WC, Haddow JE, Palomaki GE, Williams JR, Mitchell ML, Hermos RJ, Faix JD, Klein RZ, *Maternal thyroid deficiency and pregnancy complications: implications for population screening*, 7 (3) J Med Screen. 127-30 (2000), https://bit.ly/3ddcGO8.

particularly pregnant women that are hypothyroidic, or newborn infants with congenital hypothyroidism. These represent populations that should be treated by EPA as extremely vulnerable to thyroid-toxic exposures, even at low doses or for short durations. Exposures to neonics for these individuals may cause lasting neurological disabilities.

The World Health Organization recognizes iodine deficiency as the most common preventable cause of mental retardation in the world. Without adequate maternal iodine intake, both the fetus and mother are hypothyroid. Without appropriate diagnosis and treatment with iodide supplements the child may suffer abnormal neurodevelopment, in extreme cases leading to cretinism with mental retardation, deaf-mutism and spasticity. The World Health Organization estimated in 1990 that 20 million people worldwide had some degree of brain damage due to iodine deficiency experienced in fetal life. Although iodine deficiency is less common in the United States, the CDC biomonitoring data found that among women of childbearing age, 15% have low urine iodine concentrations (below 5 μg/dl) indicative of iodine deficiency. These women would be expected to be most vulnerable to the toxic effects of neonics during pregnancy. CDC reported that iodide deficiency was most common in women living below the poverty level, and people in the Southern U.S.

Because neonics cross the placenta (the DNT and other developmental tests provide evidence of trans-placental movement of the pesticide, because the pregnant dam was exposed, but the fetus displayed effects), they pose a direct risk to the fetus, and may induce hypothyroidism in the fetus and newborn. Both EPA and the National Academies identified "the fetuses of pregnant women who might have hypothyroidism or iodide deficiency" as the most sensitive population to perchlorate, a thyroid-toxic chemical that blocks iodide from forming thyroid hormone.[90] While the neonic pesticides do not act directly on iodide (as far as we know), this statement from the National Academies and EPA is just as relevant to neonics, when the fetus of a pregnant woman with hypothyroidism – possibly made worse by also having low dietary iodide – suffers 'double jeopardy' with the added risk posed by exposure to a thyroid-toxic chemical that further impairs thyroid activity.

Despite evidence that neonics are thyroid-toxic and that proper thyroid function is critical to development, EPA fails to analyze this mechanism of developmental toxicity, especially in women and children with hypothyroidism. It cannot, therefore, that removal of the child safety factor is "safe" for developing infants and children. 21 U.S.C. § 346a(b)(2)(C)(ii). EPA's removal of the FQPA factor violates the FDCA.

b. Registrant-Submitted DNT Studies Fail to Support EPA's Determination That Waiver Is "Safe"

EPA cannot determine that waiver of the child safety factor is "safe" for an additional reason: registrant-submitted DNT studies undermine this conclusion. Initially, when developing

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[90] National Research Council (NRC), Health Implications of Perchlorate Ingestion, Washington, DC: National Academies Press 178 (2005); EPA, National Primary Drinking Water Regulations: Proposed Perchlorate Rule (May 32,2019), Docket No. EPA-HQ-OW-2019-0780.

PODs for developmental toxicity, EPA relies on studies that the agency itself has deemed unreliable. More importantly, those studies demonstrate developmental toxicity at the lowest doses tested, meaning other PODs cannot reliably protect for these developmental endpoints. Accordingly, EPA lacks reliable data to depart from the default child safety factor, and its tolerances and PIDs that rely on waiver of that safety factor are unlawful.

As explained in Section II(c)(iii), the DNT is the most sensitive and reliable study for analyzing developmental neurotoxicity. It follows that where a DNT study was not submitted, or where it is of such poor quality that it fails to meet the guideline requirements and is of limited use in risk assessment, EPA lacks "reliable data" demonstrating that departure from the 10X FQPA factor is "safe." Foremost, EPA does not have a DNT study for clothianidin. But moreover, EPA classified the acetamiprid DNT study, MRID 46255619, as acceptable/non-guideline "due to the inadequacies in the assessment of motor activity and learning and memory in the offspring, and pending the evaluation [sic] the submitted positive control data." EPA stated further, "[n]o conclusions can be made on the effects of acetamiprid on learning and memory because of the high variability in the data." EPA, therefore, lacks "reliable data" on learning and memory—key endpoints for developmental neurotoxicity. Similar "non-guideline" studies relied upon by EPA include MRID 45537501, *see* Section II(a) (describing imidacloprid DNT); and MRID 46028202/47034201, *see* Section II(b) (describing thiamethoxam DNTs). EPA cannot rely on such studies as "reliable data" that neonics are "safe," and it certainly cannot make this determination regarding clothianidin without collecting a DNT study at all.

These examples highlight a fundamental problem with EPA's review of the DNTs. Where EPA identifies imperfections, they are used to discount or disregard evidence of neurotoxic effects. Nevertheless, the agency is content to rely on imperfect studies to demonstrate that neonics are "safe." This runs counter to EPA's mandate under the FQPA. EPA must have affirmative data reliably demonstrating that a child safety factor other than the statutory default of 10X is "safe." EPA inverts this burden by presuming the safety of neonics in the absence of "reliable" evidence to the contrary. EPA's inverted standard cannot support its decision that waiver of the child safety factor is "safe."

Moreover, as described at length in Section III, the DNTs do not identify true NOAELs, meaning they do not provide "reliable data" that waiver of the child safety factor is "safe." 21 U.S.C. § 346a(b)(2)(C)(ii). Examples include the imidacloprid rat DNT study, *supra* Section III(a) (showing statistically significant effects on auditory startle reflex at lowest dose and lacking morphometric data for low- and mid-dose groups); and the thiamethoxam DNT study, *supra* Section III(b) (showing statistically significant brain morphometric effects at the low- and mid-dose groups). EPA's waiver of the safety factor for these chemicals is, therefore, arbitrary and unsupported.

c. Significant Data Gaps and Uncertainties Compel Application of the FQPA 10X Safety Factor

The statutory default child safety factor is intended to account for, among other things, "completeness of the data" with respect to exposure and toxicity to infants and children. 21

U.S.C. § 346a(b)(2)(C)(ii)(II). EPA does not have complete data on the developmental toxicity of neonics, which precludes EPA from deviating from the default safety factor. The most significant examples include:

- EPA has not collected a clothianidin DNT study and has failed to explain why one is not needed. As explained in Section II(c)(iii), DNT studies are the most sensitive and reliable indicator of developmental neurotoxicity. Without this information, EPA lacks reliable data to deviate from the default FQPA safety factor for clothianidin. Waiving the child safety factor, therefore, violates the FDCA. 21 U.S.C. § 346a(b)(2)(C)(ii).
- Moreover, EPA's failure to explain why no clothianidin DNT is necessary to fully characterize the developmental effects of clothianidin is arbitrary and capricious.
- The registrant-submitted DNT studies do not show a proper NOAEL for developmental neurotoxicity of imidacloprid, *see* Section III(a), and thiamethoxam, *see* Section III(b). Without this information, EPA does not have "reliable data" that removal of the FQPA factor for these chemicals is "safe," 21 U.S.C. § 346a(b)(2)(C)(ii); its conclusion to the contrary is arbitrary and capricious.
- For acetamiprid, EPA has no data to characterize effects on learning and memory.[91] EPA failed to collect additional data or studies on DNT effects of acetamiprid, despite its conclusion that "[n]o conclusions can be made on the effects of acetamiprid on learning and memory because of the high variability in the data" in the DNT.[92] These effects are central to determining effects of pesticide exposure on the developing nervous system. EPA's conclusion that it, nevertheless, has "reliable data" that deviating from the FQPA factor is safe is arbitrary and capricious and violates the FDCA. 21 U.S.C. § 346a(b)(2)(C)(ii).
- EPA failed to collect additional data on morphological changes in the imidacloprid rat DNT.[93] EPA reviewers noted effects in high dose animals, reduced thickness of the caudate/putamen area of the brain, but Bayer had failed to include any data for the low and mid dose groups for this endpoint.[94] Bayer has had eight years to submit these data but doesn't seem to have done so. In the absence of data, the presumption should be that there may be effects in the low and mid dose groups. EPA cannot determine with "reasonable certainty" that there were no effects on brain morphology at these lower doses and, therefore, it is arbitrary and contrary to the FDCA to deviate from the default 10X FQPA safety factor. 21 U.S.C. § 346a(b)(2)(C)(ii).

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[91] EPA, Memo. ACETAMIPRID DNT STUDY (WIL-21193): Statistical Analyses for Auditory Startle Response (July 24, 2007) (Attached at p. 40 to the Data Evaluation Record, Acetamiprid Developmental neurotoxicity - rat. MRID 46255619) ("No conclusions can be made on the effects of acetamiprid on learning and memory because of the high variability in the data.").

[92] *Id.*

[93] Cheryl Bast., Data Evaluation Record: Imidacloprid, STUDY TYPE: Developmental Neurotoxicity Study – Rat, MRID 45537501 (Oct. 8, 2002), https://bit.ly/2KX7HEZ.

[94] *Id.* at Table 15 (morphometric data in offspring).

d. Application of the Required Child Safety Factor Alone Would Require Substantial Tolerance Reductions

Appropriate application of the legally mandated child safety factor would require EPA to substantially reduce neonic tolerances on foods. To determine these tolerances, EPA compares expected exposure to a pesticide to the population-adjusted dose (PAD). A risk of concern arises wherever the expected exposure exceeds 100% of the PAD (comparison represented as %aPAD). *See* EPA, Imidacloprid Acute and Chronic Aggregate Dietary Exposure and Risk Assessments at 2 (Jun. 22, 2017) ("Imid. Dietary RA") (explaining that EPA's level of concern is 100% of the cPAD or aPAD). These risks of concern necessitate tolerance reductions until the expected exposures once again fall below the PAD.

Application of the FQPA safety factor, or failure to apply it, is central to EPA's determination of the PAD. This calculation begins with the POD, the dose at which EPA has determined exposure is purportedly "safe" for the most sensitive, or "critical," endpoint. EPA then must divide this dose by a number of uncertainty factors. Commonly these include an interspecies factor used to extrapolate human effects from animal data, and an intraspecies factor used to account for variability within a species. As required in the FDCA, EPA must then apply an "additional tenfold margin of safety . . . to take into account potential pre- and post-natal toxicity and completeness of the data with respect to exposure and toxicity to infants and children." Waiving this default factor results in a PAD that is tenfold higher.

For neonics, most expected acute dietary exposures exceed 10% of the acute PAD or "aPAD," meaning application of the required 10X child safety factor would result in exposures exceeding 100% of the aPAD. The table below summarizes these exposures and the percentage of the aPAD *without* the child safety factor—all of these would exceed acceptable exposure limits if EPA applied the legally-required default 10X FQPA to protect pregnant women and children:

Active Ingredient	Population Subgroup	%aPAD
Imidacloprid, Imid. Dietary RA at 10.	General Population	38%
	Infants < 1 yr	84%
	Children 1-2 yrs	93%
	Children 3-5 yrs	73%
	Children 6-12 yrs	45%
	Youth 13-19 yrs	27%
	Adults 20-49 yrs	29%
	Adults 50-99	29%
	Females 13-49	29%

Clothianidin, Cloth. Dietary RA at 8.	All Infants	24%
	Children 1-2 yrs	28%
	Children 3-5 yrs	19%
	Children 6-12 yrs	10%
Dinotefuran, Dino. Human Health RA at 36.	All Infants	11%
	Children 1-2	12%
Acetamiprid, Acet. Human Health RA at 29.	General Population	38%
	Infants < 1 yr	69%
	Children 1-2 yrs	87%
	Children 3-5 yrs	64%
	Children 6-12 yrs	43%
	Youth 13-19 yrs	26%
	Adults 20-49 yrs	26%
	Adults 50-99	25%
	Females 13-49	26%

EPA also identifies many exposure groups for which chronic exposure to neonics exceeds 10% of the chronic PAD or "cPAD." The table below summarizes these exposures and the percentage of the cPAD, calculated without the required child safety factor:

Active Ingredient	Population Subgroup	%cPAD
Imidacloprid, Imid. Dietary RA at 10.	Children 1-2 yrs	12
Thiamethoxam, Thiam. Dietary RA at 6.	General Population	17%
	Infants < 1 yr	29%
	Children 1-2 yrs	52%
	Children 3-5 yrs	40%
	Children 6-12 yrs	23%
	Youth 13-19 yrs	14%

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	Adults 20-49 yrs	13%
	Adults 50+ yrs	14%
	Females 13-49 yrs	13%
Acetamiprid, Acet. Human Health RA at 29.	General Population	18%
	Infants < 1 yr	30%
	Children 1-2 yrs	52%
	Children 3-5 yrs	40%
	Children 6-12 yrs	25%
	Youth 13-19 yrs	15%
	Adults 20-49 yrs	15%
	Adults 50-99	15%
	Females 13-49	15%

In each case, applying the legally-mandated full child safety factor would result in risk calculations requiring tolerance reductions. Indeed, in many cases, applying even a 2x factor would establish a risk concern and compel tolerance reductions or cancellation. *See, e.g.*, Imid. Dietary RA at 10 (showing % PADs that exceed 50%). By unlawfully waiving the child safety factor, EPA fails to make legally required reductions in neonic food tolerances, putting children's health at risk in violation of the FQPA.

V. EPA'S FAILURE TO ANALYZE CUMULATIVE IMPACTS OF THE NEONIC CLASS IS UNLAWFUL

Congress amended the FDCA in 1996 to direct that EPA "shall" consider "cumulative effects" of exposure to pesticides that share a "common mechanism of toxicity." 21 U.S.C. 346a(b)(2)(D)(v). Soon after, EPA predicted that this determination would "play an increasingly important role in the evaluation of risks posed by pesticides, and will improve the Agency's ability to . . . fully protect public health and sensitive subpopulations, including infants and children." EPA, Guidance for Identifying Pesticide Chemicals and Other Substances that Have a Common Mechanism of Toxicity at 1 (Jan. 29, 1999) ("CMT Guidance"). Despite the vital importance of the cumulative effects analysis, EPA has thus far violated this statutory mandate with respect to neonics in two ways. First, to the extent it has made a common mechanism of toxicity (CMT) determination at all, it has failed to explain or support its assumption that neonics do not share a CMT. Second, neonics in fact share a CMT and EPA's failure to assess their cumulative effects violates the FQPA.

a. EPA's Failure to Explain Its CMT Determination for Neonics is Unlawful

When establishing tolerances, EPA has a mandatory duty to consider whether pesticides share a CMT. *See* 21 U.S.C. 346a(b)(2)(D). EPA has published a guidance document that describes a framework for that determination. *See generally* CMT Guidance. The framework outlines five steps: (1) identify a candidate grouping of substances that might share a CMT; (2) determine which candidate substances cause (or can be reasonably expected to cause) a common toxic effect in humans; (3) determine the toxic mechanism by which the candidates cause a common toxic effect; (4) compare mechanisms of toxicity; and (5) exclude those substances that cause a common toxic effect by different mechanisms. *Id.* at 6, 11-13.

EPA has failed to undertake any portion of this analysis with respect to neonics or make an explicit determination regarding whether neonics share a CMT. Instead, the agency has summarily dismissed this statutory requirement in the PIDs, stating that "EPA has not made a [CMT] to humans finding" for neonics and "has not assumed that" these chemicals share a CMT. C&T PID at 24; Imid. PID at 17; Dino. PID at 16; *see generally* Acet. PID (failing to mention either a CMT or cumulative effects). This explanation suggests that although EPA has undertaken no analysis to determine whether neonics share a CMT, its *de facto* assumption is that they do not.

EPA's failure to undertake this analysis is further evidenced by its response to a Freedom of Information Act (FOIA) request submitted by NRDC, Docket No. EPA-HQ-2019-004044. On March 7, 2019, NRDC requested, among other documents, "[a]ll records related to EPA's determination(s) that [neonics] do not share a [CMT]" under the FDCA. *See* FOIA Request, Attachment C at 1. During conversations between NRDC and staff in the Office of Pesticide Programs to help clarify this portion of the request, staff indicated that the documents were nonexistent because EPA had made no such determination. Indeed, over a year later, EPA has produced no documents that purport to respond to this portion of NRDC's request. *See* Interim Responses, Attachments D-F, attached.

EPA has provided no evidence or explanation in the registration review dockets for its assumption that neonics do not share a CMT, or for its refusal to make any explicit CMT finding before reaffiriming neonic tolerances in the PIDs. It has also failed to engage in the analytical process EPA itself developed for making this determination. EPA's failures render the PIDs, as well as existing neonic tolerances that rely on this statutory factor, arbitrary and unsupported by substantial evidence.

b. EPA Must Consider Neonics as a Cumulative Assessment Group

As noted above, EPA's guidance provides a step-wise framework for identifying substances that share a CMT and, therefore, must be treated as a Cumulative Assessment Group. Ultimately, however, this process turns on a determination that "two or more pesticide chemicals or other substances . . . cause a common toxic effect to human health by the same, or essentially the same, sequence of major biochemical events." CMT Guidance at 4. Neonics satisfy this foundational standard.

i. Neonics share a common thyroid-toxic mechanism

The Endocrine Society submitted expert comments to all four neonic dockets for this comment period, arguing that all the neonics should, "be reviewed together as a cumulative assessment group." Attachment B at 1. They repeat in their summary statement, "the data linking early-life neonicotinoid exposure to thyroid disruption is very concerning and EPA should conduct their review of these chemicals, incorporating the latest peer-reviewed science, as a cumulative assessment group." *Id.* at 2. This follows from the Society's first two points (discussed in Section IV(a)): that all the neonics share a common mode of action (the developing thyroid gland) and that there may be no safe level from disruptions to thyroid gland function during critical windows of development.

The recommendations of the Endocrine Society are consistent with EPA's Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity that, "chemicals that are toxicologically similar and act at the same target site" are presumed to have dose additivity.[95] The Guidance further defines dose additivity, that, "the equivalent dose is the sum of the component doses" of chemicals in a Cumulative Assessment Group. Since EPA describes all the neonics as toxicologically similar (based on their shared toxicity profile, signs and symptoms of poisoning), EPA should evaluate their risks together as a cumulative assessment group, presuming they have dose additivity. That is, exposure to 1 part imidacloprid and 1 part clothianidin will be experienced as 2 parts on the developing thyroid. EPA's Guidance notes that the equivalent dose is the sum of the component doses, scaled by each chemical's relative toxic potency. Thus, it is not necessary that each of the neonics have identical toxic potency to be presumed to have dose additivity. It is only necessary that they have a shared toxicity profile and target site. The comments of the Endocrine Society, as well as the scientific evidence detailed in these comments, argue that the chemical class of neonic pesticides do both.

If EPA adheres to its current course of action, it will be disregarding the wisdom and advice of scientific and medical experts and continuing to place America's pregnant women and children at increased risk of developmental disabilities at great cost to individuals, families, and governments.

ii. Neonics share a common neurotoxic mechanism

Structural similarities and functional groups common to all neonics result in the same mode of action in insects and mammals; they bind to a common subunit on the same receptor, the α4β2 subunit of the nAChRs.[96] This subunit is in the insect CNS, and widespread in mammal

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[95] EPA, Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity at 2 (2002), https://bit.ly/35q7nnM.

[96] *See* Tomizawa & Casida (2005), https://bit.ly/2Yoqu4a ("The neonicotinoids act as agonists at the nicotinic acetylcholine receptors (nAChRs) of insects and mammals (particularly the α4β2 subtype)."); EPA, Recognition and Management of Pesticide Poisonings: Sixth Edition at 91 (2013) ("Poisonings Manual") ("Vertebrate [α4β2] nAChRs are the primary target [of neonics]. Prolonged or chronic exposures will up-regulate the receptors without changing receptor affinity.").

(including human) central and peripheral nervous systems.[97] All neonics share the common property of being strong agonists, even displacing ACh at the receptor.[98] "The mammalian toxicity of neonicotinoids … correlates with agonist action and binding affinity at the vertebrate α4β2 nAChR, the primary target in the brain."[99] While there may be some differences in the binding kinetics across the different neonics, this does not alter the fact that the neonic family of pesticides share the same mechanism of toxicity, and the same toxicity profile (signs and symptoms of poisoning).[100]

EPA acknowledges in every neonic assessment that they all share a common mechanism of pesticidal action. *See* C&T PID at 44 ("Neonicotinoids act on the central nervous system of insects, causing irreversible blockage of the postsynaptic nicotinic acetylcholine receptors (via a selective agonistic mechanism)."); Acet. PID at 4 ("All neonicotinoids function by binding to nicotinic acetylcholine receptors in the post-synaptic neurons of an insect's central nervous system."); Imid. PID at 4 (imidacloprid "causes irreversible blockage of the postsynaptic nicotinic acetylcholine receptors"); Dino. PID at 4, 47 (dinotefuran "acts on the neonicotinoid acetylcholine receptors (nAChRs) of the central nervous system" and is a "nicotinic acetylcholine receptor (NACHR) competitive modulator"). Because mammals, including humans, share with insects the same nAChR subunit targeted by neonics, neonics share a common mechanism of toxicity.

Interference with the mammalian α4β2 nAChR, caused by all neonics, produces common toxic effects on the neurological system, including developmental neurotoxicity and symptoms of poisoning. EPA defines a "toxic effect," for purposes of CMT analysis, as an effect that is known *or "can reasonably be expected"* to occur in humans. CMT Guidance at 3. Based on poisoning data, neonics are known to have common toxic effects in humans. EPA has explained:

> Most clinical effects are based on excessive nicotinic stimulation. Patients have presented with disorientation, confusion and agitation—severe enough to require sedation—headache, drowsiness, dizziness, weakness, tremor and, in some situations, loss of consciousness.[101]

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[97] Posadas et al. (2013), doi: 10.2174/1570159X11311030005, https://bit.ly/3c5C7kr.

[98] EPA, Clothianidin fact sheet. Mechanism of Pesticidal Action at 17 (2003), https://bit.ly/2WnbXmt; Tomizawa & Casida (2008), https://bit.ly/2SxuFXs.

[99] Tomizawa & Casida (2005), https://bit.ly/2Yoqu4a.

[100] Sánchez-Bayo & Tennekes (2020), doi: 0.3390/ijerph17051629, https://bit.ly/2xuV68W; Posadas et al. (2013), doi: 10.2174/1570159X11311030005, https://bit.ly/3c5C7kr; Simon-Delso et al. (2015), doi: 10.1007/s11356-014-3470-y, https://bit.ly/3djKARn.

[101] Poisonings Manual at 91 (citing Agarwal R, Srinivas R, *Severe neuropsychiatric manifestations and rhabdomyolysis in a patient with imidacloprid poisoning*, 25 (7) Am J Emerg Med. 844-45 (Sep 2007)); David D, George IA, Peter JV, *Toxicology of the newer neonicotinoid insecticides: imidacloprid poisoning in a human*, 458

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These are classic symptoms of poisoning by a neurotoxic agent. EPA's own poisoning reports also demonstrate substantial overlap among the symptoms that are observed from poisoning with different neonics. *See* Section II(b)(ii). Given this evidence of common toxic effects in humans, EPA's assumption that neonics do not share a CMT is untenable and arbitrary.

Moreover, registrant-submitted studies have also demonstrated developmental effects as a result of neonic exposure. In DNT studies for imidacloprid, thiamethoxam, and acetamiprid, statistically significant effects on the auditory startle reflex were observed. *See* Section III. The same studies for imidacloprid and thiamethoxam also detected significant changes in morphometric brain data. *See* Sections III(a), (b). These data indicate that neonics are having common effects on the nervous system, that can reasonably be expected to impact neurological functioning in humans. These effects further support a determination that neonics share a CMT.

VI. EPA'S AGGREGATE EXPOSURE ASSESSMENT IGNORES IMPORTANT DEGRADATES AND THEIR TOXICITY

The FDCA requires EPA to consider "aggregate exposure to . . . pesticide chemical residue[s], including all anticipated dietary exposures and all other exposures for which there is reliable information." 21 U.S.C. § 346a(a)(2)(A)(ii). This aggregate exposure analysis includes not only the pesticide itself, but "other related substances" from all "non-occupational sources," *id.* § 346a(a)(2)(D)(vi). Non-occupational sources include drinking water. *See, e.g.*, Imidacloprid, Order Denying Objections to Issuance of Tolerance, 69 Fed. Reg. 30,042, 30,072 (May 26, 2004) (collecting sources and explaining that the FDCA "requires EPA, in making a section 408 safety finding, to consider all exposures to the pesticide and related substances, whether the exposure is from food, water, or other [non-occupational] sources").

Pesticide degradates are among the "other related substances" which EPA must include in its tolerance assessment. EPA has implicitly acknowledged this in the PIDs. *See, e.g.*, EPA, *Imidacloprid: Human Health Draft Risk Assessment for Registration Review* 22 (Jun. 22, 2017) (including imidacloprid urea, guanidine, and olefin in the water residue profile). EPA has also incorporated pesticide degradates found in drinking water into its aggregate assessment in other tolerance actions. *See, e.g.*, Proposed Order Granting Objections to Tolerances and Denying Request for a Stay, 76 Fed. Reg. 3,422, 3,442 (Jan. 19, 2011) (explaining that tolerance assessment for sulfuryl fluoride must include fluoride, a degradate of sulfuryl fluoride added to drinking water); *see also* EPA Office of Pesticide Programs, *Estimating the Drinking Water Component of a Dietary Exposure Assessment* 18 (Nov. 2, 1999) ("[U]sefulness of the [water] monitoring data in a risk assessment" depends partly on "inclusion of important metabolites and degradates.").

Accordingly, EPA must consider the neonic degradates described below in its aggregate exposure assessments. EPA may only set a tolerance if it has "reasonable certainty" that

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(5) Clin Toxicol (Phila) 485-86 (Jun-Aug 2007), 10.1080/15563650701338229; Huang NC, Lin SL, Chou CH, Hung YM, Chung HM, Huang ST, *Fatal ventricular fibrillation in a patient with acute imidacloprid poisoning*, 24 (7) Am J Emerg Med.883-85 (Nov 2006)), 10.1016/j.ajem.2006.03.008.

aggregate pesticide exposure will avoid all harm to human health. 21 U.S.C. § 346a(a)(2)(A)(ii). Without considering the exposure potential and toxicity of these degradates, EPA's determination of "reasonable certainty" of no harm is unsupported, arbitrary, and capricious.

a. EPA's Aggregate Exposure Assessments Must Consider the Enhanced Toxicity of Degradates Lacking the Nitro- or Cyano- Functional Group.

In its Imidacloprid Drinking Water Exposure Assessment, EPA explains that its modeling "assumes that toxicity of imidacloprid parent is equal to each of the constituents of its residues." EPA, Drinking Water Exposure Assessment in Support of the Preliminary Risk Assessment for the Registration Review of Imidacloprid at 3 (Dec. 22, 2016) ("Imid. Drinking Water RA"). EPA, however, offers no citation or evidence to support this assumption, and research indicates that degradates lacking the nitro- or cyano-groups of parent neonics can be substantially more toxic than the parent. EPA's assumption—and the tolerances that rely on it—are, therefore, arbitrary and unsupported by substantial evidence.

A notable example is desnitro-imidacloprid ("desnitro"), which EPA identifies as a "residue of concern" for imidacloprid. Imid. Drinking Water RA at 3. EPA explains that desnitro is "expected to contaminate ground and surface waters" *id.* at 8, and characterizes it as a "major metabolite" of imidacloprid in both aerobic and anaerobic aquatic environments, *id.* at 6. Indeed, recent research from the U.S. and Canada demonstrates that both neonic parent compounds and their degradates can extensively contaminate finished drinking water in areas of neonic use.[102] For example, researchers at the U.S. Geological Survey "ubiquitously detected" neonics in drinking water at the University of Iowa,[103] and, in a second round of sampling, also found two neonic degradates—desnitro and imidacloprid-urea—in more than half of the samples collected.[104] Even the most effective form of water treatment, granular activated carbon (GAC), is not guaranteed to remove all neonics.[105]

Notably, desnitro is formed when an imidacloprid molecule loses its nitro-group, the functional group that plays a central role in lowering the binding affinity of imidacloprid to mammalian nAChRs.[106] In other words, loss of the nitro group can be expected to make desnitro

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[102] Klarich KL, Pflug NC, DeWald EM, Hladik ML, Kolpin DW, Cwiertny DM, LeFevre GH, *Occurrence of Neonicotinoid Insecticides in Finished Drinking Water and Fate During Drinking Water Treatment*, 4 (5) Environmental Science & Technology Letters (Apr. 5, 2017), https://bit.ly/2KWrOU4; Klarich-Wong KL, Webb DT, Nagorzanski MR, Kolpin DW, Hladik ML, Cwiertny DM, LeFevre GH, *Chlorinated Byproducts of Neonicotinoids and Their Metabolites: An Unrecognized Human Exposure Potential?*, 6 Environmental Science & Technology Letters 98-105 (Jan. 14, 2019), https://bit.ly/2RYBiSm; Sultana T, Murray C, Kleywegt S, Metcalf CD, *Neonicotinoid Pesticides in Drinking Water in Agricultural Regions of Southern Ontario, Canada*, 202 Chemosphere 506-513 (Jul. 2018), https://bit.ly/3czD3gM.

[103] Klarich et al. (2017), https://bit.ly/2KWrOU4.

[104] Klarich-Wong et al. (2019), https://bit.ly/2RYBiSm.

[105] Klarich et al. (2017), https://bit.ly/2KWrOU4.

[106] Tomizawa and Casida (2005), https://bit.ly/3bwIsFg.

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more likely to bind to human cells and, therefore, more toxic to people.[107] As a result, desnitro is up to *317 times more toxic* to mammals than imidacloprid.[108]

Desnitro exemplifies why EPA cannot simply assume that toxicities of neonic degradates are equal to their parent compounds. EPA must apply a toxicity adjustment factor to account for desnitro's increased toxicity.[109] Its unsubstantiated assumption leads the agency to set tolerances above the levels above that the FQPA requires to protect human health. These tolerances are unlawful, arbitrary and capricious.

b. EPA's Aggregate Exposure Assessments Must Consider Chlorinated Neonic Compounds in Drinking Water.

Research by the U.S. Geological Survey indicates that when neonic-contaminated water passes through common chlorination drinking water treatment systems, the treatment can modify the chemical structure of both neonic parent compounds and degradates—forming "chlorinated disinfection byproducts." [110] The study authors note that while "[t]he mammalian toxicity of [these] transformation products . . . remains unknown. . . . [s]everal transformation products identified (CLO 239a, CLO 239b, CLO-THX-H 270, IMI 246, THX-H 248, DN-IMI 245 and DN-275 IMI 279) appear to lose the nitro-group through chlorination or hydrolysis, and/or gain one or more chlorines—both characteristics that may increase mammalian toxicity."[111]

Because 98% of drinking water treatment systems in the United States use some form of chlorination,[112] it is likely that chlorination byproducts will form where neonic-contaminated water is present and other forms of filtration or purification are not used. Given that these compounds exhibit characteristics suggesting they are more toxic to human health than their pre-transformation compounds, EPA must consider these compounds in its aggregate exposure analyses.

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[107] Klarich-Wong et al. (2019), https://bit.ly/2RYBiSm ("toxicological profiles of neonicotinoid transformation products formed via degradation processes may be different from that of the parent compounds, particularly when the nitro- or cyano-groups are removed").

[108] *Id.* (citing Tomizawa & Casida (2005), https://bit.ly/2Yoqu4a).

[109] *E.g.*, EPA, Reregistration Eligibility Decision for Malathion at vii (May 2009), https://bit.ly/3daw0eV (applying a 61X toxicity adjustment factor to account for the toxicity of malaoxon compared to the parent compound).

[110] Klarich-Wong et al. (2019), https://bit.ly/2RYBiSm.

[111] *Id.*

[112] Scheer R & Moss D, *All's Well? Is Chlorine the Best Option for Purifying Drinking Water?*, Scientific American (Apr. 15, 2013), https://bit.ly/3bvsnzy.

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c. Failing to Address the Sources of Neonic Drinking Water Contamination Imposes Burdens on Rural Communities

Water systems facing elevated levels of neonics may need to install granulated activated carbon (GAC) filters to reduce levels of this pesticide. "The primary purpose of the GAC system is to reduce total organic carbon levels in the treated water and prevent formation of disinfection by-products. The secondary purpose is pesticide removal."[113] Initially, GAC is not guaranteed to remove all neonics.[114] Moreover, installing and maintaining an effective GAC system can be a large expense. The small systems taking water from areas surrounded by agricultural lands on which neonics are used may be most vulnerable to the contamination and be faced with paying these high costs. For example, the Mt. Orab water system in Brown County, Ohio produces 372,000 gallons of drinking water per day for about 3,600 people. To treat this water, Mt. Orab spends $50,000 per year just on carbon replacement for its GAC filters; that figure does not include the cost of purchasing the system or performing other needed maintenance.[115] EPA cannot require, and should not expect that the most vulnerable water treatment facilities – the smaller ones serving populations in areas of high pesticide use – will have tap water treatments that can reliably and effectively remove neonic pesticides, neonic metabolites such as desnitro-imidacloprid, and neonic-derived chlorinated disinfection byproduct.

VII. EPA'S ACUTE DIETARY RISK ASSESSMENTS ARE INADEQUATE

EPA's acute dietary assessments calculate acute risks of concern by comparing estimated exposure to the aPAD; if exposure exceeds the aPAD, EPA must take action to reduce exposure.[116] When analyzing acute risks of neonics, EPA determines that there are no risks of concern because estimated exposure falls below the aPAD. However, the figure used to estimate exposure represents only the 95th exposure percentile. In other words, five percent of the population—roughly 16 million people nationwide—are exposed to neonics at levels that exceed the level analyzed by EPA.

Initially, EPA cannot determine with "reasonable certainty" that current tolerances will result in "no harm" without quantifying or considering risk to the 5 percent of people most exposed to neonics. 21 U.S.C. § 346a(b)(2)(A)(ii). The agency's determination that tolerances are nonetheless "safe," therefore, violates the FDCA.

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[113] State of Ohio Environmental Protection Agency, Biological and Water Quality Study of the White Oak Creek Watershed, 2006; Highland and Brown Counties, (Dec. 12, 2008), https://bit.ly/2YsoKqr.

[114] Klarich et al. (2017), https://bit.ly/2KWrOU4.

[115] State of Ohio Environmental Protection Agency, Biological and Water Quality Study of the White Oak Creek Watershed, 2006; Highland and Brown Counties (December 12, 2008), https://bit.ly/2KZyWPp.

[116] EPA, General Principles for Performing Aggregate Exposure and Risk Assessments at 22 (Nov. 28, 2001), https://bit.ly/3cJzLaX.

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Moreover, EPA failed to explain why it selected the 95th percentile, as opposed to the 99th percentile or some other number, to characterize these risks. In previous risk assessments, it analyzed exposure at 99.9th percentile.[117] Its decision to exclude roughly 16 million people from its acute risk analysis is, therefore, arbitrary and unsupported.

One exposure, in particular, demonstrates the danger of EPA's decision. The acute dietary risk assessment for imidacloprid concluded that the 95th exposure percentile for children 1-2 years old are exposed at *93% of the aPAD*. Imid. Dietary RA at 9. These findings indicate that hundreds of thousands of children—possibly millions—are being exposed at over 93% of the level that would trigger a risk of concern. In other words, many of these high-exposure populations are likely exposed to levels that EPA has determined are not "safe." EPA must implement a more conservative measure of exposure to account for these high-exposure populations or, at a minimum, explain its decision to exclude those populations from its analysis. Its failure to do so is arbitrary and unsupported by substantial evidence.

VII. CONCLUSION

EPA's tolerances for imidacloprid, thiamethoxam, clothianidin, dinotefuran, and acetamiprid are arbitrary and capricious and violate the FDCA's mandate. 21 U.S.C. § 346a(b)(2)(A)(i). Accordingly, EPA must grant NRDC's petition and revoke all tolerances for neonics on or in food. Moreover, EPA must cancel any registered use for which it cannot provide substantial evidence that the use satisfies the FIFRA standard. 7 U.S.C. § 136a(c)(5)(C).

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[117] *See, e.g.*, EPA, Reregistration Eligibility Decision for Dichlorvos at 150 (July 31, 2006).

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