Notice of Objection to PMRA's Re-evaluation Decision RVD2021-05, Imidacloprid and Its Associated End-use Products

Submitted by Friends of the Earth Canada
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The Proposed Re-evaluation Decision PRVD2016-20, Imidacloprid, called for the phase-out of all the agricultural and a majority of non-agriculture uses of imidacloprid due to unacceptable risk to aquatic organisms. The report underwent a 120-day consultation period ending on 23 March 2017. Following a four-year delay, the final Re-evaluation Decision was released May 2021, and reports a dramatic reversal of position, largely due to an influx of new industry-provided data and analyses. Health Canada has now determined that continued registration of most products containing imidacloprid is acceptable.

Friends of the Earth submits its Notice of Objection based on its concern with PMRA's **inadequate assessment of research on human health effects of imidacloprid despite an unusual four year interval prior to its final decision.**

Friends of the Earth finds the absence of comprehensive current science on human health impacts unacceptable. We have undertaken a preliminary assessment of such science and provide our references which we believe, taken as a whole, point to the need for precautionary action in banning the use of imidacloprid and immediate action to reduce the MRL for imidicloprid to zero. Further, we believe that the delay of four years before PMRA provided its final decision was more than adequate time for a substantial and up to date review of human health research including cumulative exposure through both diet and the environment. In Appendix A, we review PMRA's references to human health considerations in RVD2021-05 and find it remarkably limited to the point of negligence on such an important matter.

Overview of Preliminary Assessment

Considering available information about the current rate of human exposure through food and water, Friends of the Earth believes that the ubiquitous nature of neonics in our food and water systems poses the risk of significant cumulative exposure through both diet and environment.

The detection of neonic residues and their metabolites appears to be directly linked to bioaccumulation in humans and other invertebrates, increasing the risk of chronic health defects due to long-term exposure.

There is mounting evidence that active neonicotinoid metabolites may pose a far greater risk to human health, which may help to explain observations of adverse effects in mammalian systems.

Multiple studies suggest that chronic exposure to neonics and their metabolites can initiate toxic effects at low levels, in absence of acute poisoning scenarios. These include mechanisms acting at the level of reproduction, neurodevelopment, genetic damage and liver metabolism. These metabolites include various by-products of direct enzymatic processing by human organs, as well as bacteria and fungus present in the human gut and crop soil.

Friends of the Earth reviewed RVD2021-05 Imidacloprid Final Decision to assess its treatment of human health concerns and finds it shocking in its limitations. The unusual four year period between the conclusion of the official consultation and the publication of PMRA's Final Decision should have allowed for a detailed assessment of global bio-monitoring and other research on human health impacts.

Preliminary Assessment of Imidicloprid and Human Health Impacts

There are limited studies directly addressing impacts of neonics on human health. One 2017 review, cited in RVD2021-05, found eight studies that directly address human neonic exposure over the period 2005-2015, only half of which looked at environmental exposure as opposed to self-poisoning[i]. However, more recently, multiple reviews have called for more thorough research into the impacts of neonics on human health[ii,iii,iv], given the present gaps in knowledge and a growing body of research suggesting they may be biologically harmful to humans and animals.

Despite this, the acceptable daily intake (ADI) recommendations for different countries vary widely[v] and there is concern that these low doses may still be sufficient to have significant impacts on human and mammalian health.

When we considered the current rate of human exposure through food and water, Friends of the Earth believes that the ubiquitous nature of neonics in our food and water systems poses the risk of significant cumulative exposure through both diet and environment.

In *food products*, neonics are used to treat seeds or plant surfaces, are taken up by the roots or leaves and penetrate the plant tissues, including foliage and the interior of fruits and vegetables[vi]. This not only increases the opportunity for cumulative exposure (i.e., through pollen, fruit, leaves of the same plant) but makes removal of trace neonicotinoid residues nearly impossible through normal washing or surface treatment.

A survey of US-purchased food found all fruit and vegetable samples (except nectarine and tomato) and 90% of honey samples were detected positive for at least one neonicotinoid; 72% of fruits, 45% of vegetables, and 50% of honey samples contained at least two different neonicotinoids in one sample.[vii]

Other surveys in both the US and other countries such as Belgium, Japan, Turkey and China have detected neonic residue in commonly consumed foods. Although detection levels vary between studies, in most cases residues of at least one neonic chemical were detected in >50% of tested produce samples, in some cases reaching up to ~80% detection rate.[viii, ix] Although most of these residue concentrations did not exceed the maximum residue level (MRL) in their respective countries, some commodities such as tea leaves[x], tomatoes, grapes and strawberries approached or exceeded these limits.[xi]

Although there is a lack of surveys conducted in the Canadian marketplace, a similar detection profile is likely given these rates were consistent for both locally grown and imported commodities across studies.

In *drinking water and water systems*, in Canada, imidacloprid, clothianidin, and thiamethoxam were detected in over 90% of streams sampled, with two locations exceeding Canadian freshwater guidelines with concentrations above 230 ng/L in 75% of samples.[xii]

Clothianidin, imidacloprid, and thiamethoxam were ubiquitously detected in finished water samples collected in Iowa, at concentrations ranging from 0.24 to 57.3 ng/L .[xiii] Other water samples collected in the US and Australia display levels as high as 4.5ug/L in unfinished drinking water.[xiv]

Cause for concern based on findings of bio-monitoring studies not cited in RVD2021-05 unless otherwise noted

Neonicotinoids are well absorbed by humans after oral intake and are mainly excreted in urine, with urine samples being the primary method for assessing human neonic exposure.

Examination of over 3000 urine samples from the U.S. general population revealed children 3 years of age and older displayed significantly higher levels of neonic metabolites compared to other age groups, leading the authors to conclude that 49.1% of the U.S. general population 3 years of age and older had been recently exposed to neonicotinoids.[xv] (cited in RVD2021-05)

Nimako et. Al reported detection of 7 neonicotinoids and 3 neonicotinoid metabolites in a total of 75 human urine samples collected from healthy volunteers (nonfarmers, aged 13–80 yr) in Kumasi, a city in Ghana, with concentrations reaching up to 211.62 µg/L.[xvi]

A variety of studies in Japan[xvii] and China [xviii, xix] have detected significant levels of neonics and/or their metabolites in urine samples collected from both rural and urban populations. However, more recent studies have also detected significant levels of neonics in other human tissues and fluids such as serum[xx], hair[xxi], breast milk[xxii] and saliva.

Zhang et al. measured concentrations of six neonics and three corresponding metabolites in 188 paired saliva and periodontal blood samples collected from South China[xxiii]. Neonics and their metabolites were frequently detected (68–94%) in paired saliva and periodontal blood, with median levels of 0.01–0.99 ng/mL. Levels of neonicotinoids in paired samples were positively associated with 8-Hydroxy-2'-deoxyguanosine, a marker of oxidative stress.

In a study examining a cohort of children aged 3-14 years old, Laubscher et al. found that that their CSF and plasma samples were positive for at least one neonicotinoid, with 64% and 93% containing more than one neonicotinoid, respectively. [xxiv]

Furthermore, after oral administration of neonics in mice (0.6mg/kg bw/ day), imidacloprid and five of its metabolites were detected in the brain, testis, lung, kidney, white adipose tissue, blood,

liver, and pancreas, indicating a differential metabolism and accumulation of neonicotinoids and their metabolites in a variety of tissues.[xxv]

Thus, detection of neonic residues and their metabolites appears to be directly linked to bioaccumulation in humans and other invertebrates, increasing the risk of chronic health defects due to long-term exposure.

While current research is confined to small populations in particular geographic regions, it emphasizes the need for large-scale bio-monitoring studies in both Canada and other countries to assess the population-level risk posed by agricultural reliance on neonics. It supports Friends of the Earth's call for precautionary action in banning the use of imidacloprid and reducing the current Canadian MRL to zero.

Basis for concern

The main rationale used for neonicotinoid safety and use is that it selectively targets signalling the insect nervous system. This is attributed to preferential and irreversible interaction with insect nicotinic acetylcholine receptors (nAChRs), whereas these compounds tend to have a lower affinity for mammalian nAChRs.[xxvi]

However, there is mounting evidence that active neonicotinoid metabolites may pose a far greater risk to human health, which may help to explain observations of adverse effects in mammalian systems despite this selectivity gap.

These metabolites include various by-products of direct enzymatic processing by human organs, as well as bacteria and fungus present in the human gut and crop soil.[xxvii] They can also involve products of abiotic processes such as chlorination during drinking water treatment, hydrolysis and photolysis. This often results in modification of cyano- and nitro- functional groups on the parent compound that can increase their toxicity to humans and other vertebrates.[xxviii] Furthermore, it has been shown that co-exposure to neonicotinoids and synergists such as Piperonyl butoxide can increase their toxic effects.[xxix]

Beyond potential interaction with the mammalian nervous system, the distribution and levels of such metabolites may translate into adverse effects on a range of physiological systems.

Considering the potential mechanisms of harm: acute poisoning, toxic effects at low levels, neurological effects, endocrine/reproductive/developmental effects, metabolic effects, fetal exposure and developmental effects

Acute poisoning symptoms of neonicotinoids have been well documented, including symptoms such as nausea, vomiting, abdominal pain, headaches, agitation, confusion, hypertension and respiratory failure. [xv]

Estimates of current dietary and other exposure in countries such as Japan and the US have fallen well below the maximum recommended daily intake (RDA) provided by respective regulatory bodies.

However, multiple studies suggest chronic exposure to neonics and their metabolites can initiate toxic effects at low levels, in absence of acute poisoning scenarios. These include mechanisms acting at the level of reproduction, neurodevelopment, genetic damage and liver metabolism, all of which have been thoroughly reviewed and are briefly summarized here. None are cited in RVD2021-05.

Neurological effects:

Despite the aforementioned low affinity for mammalian AChRs, neonics and their metabolites have demonstrable impacts on the central nervous system (CNS). *Desnitroimidacloprid*, a toxic metabolite of imidacloprid, has been shown to have affinity for mammalian AchRs on par with that of nicotine.[xxx]

Furthermore, low levels (10uM) of clothianidin, acetamiprid and thiamethoxam have been shown to be potent modulators of current through AChRs in vitro. This means that although they did not serve as primary receptor agonists, they were able to increase or decrease receptor activity in response to their endogenous ligand (acetylcholine), which would translate into interruption of Ach-mediated neuronal signalling in vivo.[xxxi]

Katic et al. found that oral 28-day exposure to low doses (0.6-2 mg/kg bw/day) of imidacloprid in rats resulted in detectable levels in plasma and brain tissue that directly induced DNA damage, particularly in brain tissue, with slight changes in plasma oxidative stress parameters.[xxxii]

Nakayama et al. found that acetamiprid and imidacloprid-exposed mice (5mg/kg/day, below NOAELs) exhibited significant increases in the number of activated microglia in the developing hippocampus as well as decreased neurogenesis, suggesting an impact of neonics on neurodevelopment in neonates.[xxxiii]

Abd-Elhakim et al. found that exposure to IMI even at very low concentrations (1 mg/kg bw/day) could induce multiple neurobehavioral aberrations and neurotoxic impacts, including deficits in sensorimotor functions, reduced Levels of neurotransmitters, Oxidative damage of brain tissues and varying degrees of neural degeneration.[xxxiv]

Low doses of acetamiprid and imidacloprid were sufficient to induce cytotoxic effects in rat neonate cerebellar neurons, suggesting potential adverse effects on the developing brain.[xxxv]

Endocrine/Reproductive/developmental effects

Low-dose imidacloprid exposure (0.25 – 2 fold ADI of 0.06mg/kg) caused sperm abnormalities through affecting on the spermiogenesis in testis. Inhibition of CYP3A4 activity by imidacloprid largely contributed to its sperm toxicity.[xxxvi]

Six-week-old male ICR mice were administered imidacloprid (3, 10 and 30 mg/L) for 10 weeks showed impaired testicular morphology, and the levels of serum testosterone and the expression of androgen receptor (AR) decreased significantly.[xxxvii]

Exposure of Hs578t cells to environmental concentrations (0.03 – 0.3 uM) of imidacloprid and thiacloprid increased *CYP19* expression and aromatase catalytic activity, similar to signalling cascades observed in patients with hormone-dependent breast cancer.[xxxviii]

In a study by Hafez et al. comparing farm workers (n=35) to healthy volunteers (n=25), researchers found a significant negative correlation between sperm concentration/motility and serum or seminal imidacloprid, its main metabolite 6-chloronicotinic acid (6- CINA) and cotinine. [xxxix]

Kapoor et al. found that in mice a 20 mg/kg/day dose produced significant alterations in the levels of luteinizing hormone (LH), follicle stimulating hormone (FSH) and progesterone in female mice as well as altered ovarian morphology. [xl]

Metabolic effects

After 30 days of exposure to neonicotinoids (1/200 LD50, 0.5mg/kg bw/day), mice showed signs of amino acid metabolism disorders (especially elevated branched chain amino acids and phenylalanine), resulting in lipid accumulation and oxidative stress in the liver. [xli]

Zheng et al. found that low dose imidacloprid (5mg/kg/day) was sufficient to disrupt normal metabolic profile in the liver and hippocampus, while higher doses of 20mg/kg/day were sufficient to induce significant toxicity symptoms such as piloerection, tremor, diarrhea and salivation. In addition, they observed increased weight of brain and liver and tissue necrosis in the high-dose group.[xlii]

Studies by Sun et al. found that very low doses of imidacloprid (0.6-6 mg/kg bw/day) were sufficient to significantly increase the effects of high fat feeding on body weight gain and adiposity, in addition to promoting impaired glucose metabolism and insulin resistance.[xliii]

Fetal exposure and developmental effects

It is well known that the fetal brain is highly susceptible to chemical toxicity compared to adults, due to a combination of factors including an underdeveloped blood brain barrier, active neurogenesis, and formation of neural circuits.[xliv, xlv, xlvi] Furthermore, the growing fetus is especially vulnerable to environmental toxins that can have variable deleterious effects, such as interfering with cell proliferation rate, altered biosynthetic pathways and abnormal cellular or tissue interactions.[xlvii]

Previous studies have reported that the offspring of mice exposed to NNs during the gestational period (as low as 0.5mg/kg maternal exposure) have delayed behavioral development in early life, as well as abnormalities in anxiety-like and social behaviors in adulthood.[xlviii, xlix, l, li, lii] Keil et. al observed a small yet significant association between prenatal exposure to IMI and ASD (OR = 2.0) among children of mothers who self-identified as “frequent users” of flea and tick medicines containing IMI during pregnancy.[liii]

Conclusion

Friends of the Earth fears that PMRA has been recycling the registrants' limited view and research on neonics' impacts on human health and, without independent science and scientists able to work on imidicloprid and other neonics, Canadians and their children and grandchildren are suffering from twenty years of exposure to this class of pesticides called neonicotinoids including imidacloprid, thiamethoxam and clothianidin.

The geographic limitations to research results identified in our preliminary assessment demonstrate the need for Canadian investment in research to address food and water contamination by neonicotinoid pesticides and to establish systematic bio-monitoring. Such investment should be made available for peer-reviewed science by researchers independent of PMRA and registrants.

We understand the remedy available under a Notice of Objection is establishment of an Independent Review Panel. Further, we believe that our preliminary assessment, as introduced in this notice, raises scientifically founded doubt about the validity of PMRA's evaluation of human health risks of imidicloprid under **RVD2021-05.** We believe that precautionary action across the class of neonicotinoids is justified and therefore make two further recommendations (3 & 4 below).

Friends of the Earth calls for:

1) Immediate action by Health Canada to establish an Independent Review Panel, with no PMRA representation, to address human health impacts of imidacloprid and its metabolites.
2) As a precautionary measure, the Canadian Maximum Residue Level (MRL) level for imidacloprid should be reduced to zero.
3) Significant research funds should be provided for independent scientists to conduct peer-reviewed research on neonicotinoid pesticides, a systematic bio-monitoring program should be established and delivered by Health Canada (outside of PMRA) with Environment Canada's co-operation.
4) A Scientific Assessment should be conducted by Environment Canada as a prelude to listing neonicotinoid pesticides as toxic substances for the purpose of regulating under the Canadian Environmental Protection Act (CEPA).

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ANNEX ONE
Review of human health references in RVD2021-05 Imidacloprid Final Decision

Page 2, Science Evaluation Summary:
"An evaluation of the human health risks associated with imidacloprid has concluded that all uses are acceptable for continued registration with revised label instructions. Some occupational scenarios require revised label directions. Also, some spot-on pet product labels must be brought to current standards. Updates to the assessment can be found in the Science Evaluation Update and Appendix V.

An evaluation of available scientific information found that most uses of imidacloprid products meet current standards for protection of human health and the environment and have acceptable value when used according to revised conditions of registration, which includes new mitigation measures."

Page 3, Risk Reduction Measures Adopted for Imidacloprid's Risk to Human Health:

- Changes to personal protective equipment (PPE) and engineering controls for seed treatment uses.
- Update current ventilation statement on the Temprid SC label to include the requirement that ventilation must also occur during application to mitigate inhalation exposure of applicators, as well as any occupants that may enter treated areas following the 6-hour re-entry interval.
- Update commercial labels to current standards by including restricted entry intervals and/or spray drift precautions when they are absent, and clarification that the use in greenhouses is not allowed for uses only registered for outdoor areas.

Page 104-5, Health Canada's response to a comment noting that reports of human intoxication from Dr. Kumiko Taira were missing from the final decision:
"Health Canada carefully considers published, peer-reviewed literature during the course of a re-evaluation which includes available human data such as case reports and epidemiological studies. As presented in the PRVD for imidacloprid, published case reports that explored the potential health effects of imidacloprid exposure (among other pesticides) in human populations were briefly discussed. Overall, the findings of all of the available human studies were often limited by small numbers of cases and lacked characterization of exposure conditions (such as the concentration of pesticide and the duration of exposure)."

Given the lack of specific details presented in these reports, Health Canada concluded from a scientific perspective, that these reports were of limited quality and did not provide information to add to the weight-of-evidence for risk assessment purposes."

Page 105: Health Canada notes that both the Taira study and an additional Kimura-Kuroda study were unavailable at the time of the assessment of human health risks and provided insufficient quality to be included later on. **See also:** Page 110 for another study from Tokyo Women's Medical University that was disregarded.

Page 111, Health Canada's response to a comment voicing concern that the effects of imidacloprid on pregnant women and their babies was not fully considered:

"As was stated in the PRVD for imidacloprid, the toxicological database was considered complete and consisted of the full array of toxicity studies currently required for the human health risk assessment. With respect to the completeness of the toxicity database as it pertains to the exposure of and toxicity to infants and children, the database contains the full complement of required studies."

Page 113, the PMRA will consider conducting a cumulative effects review of neonics:
"As noted in PRVD2016-20, upon completion of the ongoing re-evaluations of other chemicals in the neonicotinoid class of pesticides (namely thiamethoxam and clothianidin), it will be determined whether a cumulative effects assessment is necessary, taking into account the ability of neonicotinoids to bind to nicotinic acetylcholine receptors. The cumulative effects assessment will be undertaken according to the process outlined in SPN2018-02. In the meantime, the current human health risk assessment of imidacloprid is considered complete."

Page 115, Health Canada's response to concerns of farm worker exposure to imidacloprid:

"As indicated in the PRVD (2016-20) and Section 2.1, the health risks to seed treatment workers are shown to be acceptable provided that the appropriate personal protection equipment instructions and engineering controls are updated on labels."

Page 116, Health Canada's comments on maximum residue limits for imidacloprid:
"As a result of imidacloprid re-evaluation, no dietary risks of concern were identified from exposure to imidacloprid through food and drinking water. Therefore, there will be no amendments to the currently established MRLs as part of the re-evaluation decision. That is, the current Canadian MRLs for imidacloprid will be maintained."