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By Email: PMRA.publications@hc-sc.gc.ca

Submission to

Health Canada, Pest Management Regulatory Agency

regarding

Proposed Re-evaluation Decision PRVD2016-20

Imidacloprid

About Us

Prevent Cancer Now (PCN; www.preventcancernow.ca) is a national Canadian organization working to eliminate preventable contributors to cancer. PCN conducts research, provides scientific analysis and input to governmental consultations, and conducts public education to minimize hazardous exposures to agents that can contribute to the development of cancer. PCN scientists and medical experts provide information based on a broad understanding of the science of contributors to cancer. Of course, contributors to good health (e.g. healthy food) and to the development of cancer (e.g. toxicants in air, water and food) also affect incidence and prevalence of other chronic diseases.

Overview

PCN supports the phase-out of imidacloprid, and of all neonicotinoid-like insecticides (see Table 1). We note that three related chemicals are not presently labelled in Canada, and should not be entertained – nitenpyram, nithiazine and fipronil. Concerted actions on all of these chemicals are necessary because of:

1. the chemical properties and common metabolites shared by these systemic insecticides (meaning the chemicals permeate the plant); and
2. the high probability that only concerted action will avert similar chemicals being substituted and negating the intention of an imidacloprid phase-out.

These pesticides are very persistent, with insecticidal activity lasting one or even two seasons (e.g. injectable tree treatments). Although "half-life" generally refers to a parent compound, the large number of metabolites take years to break down and dissipate. Some metabolites are more toxic to mammals or other creatures than the parent compound; some break down into insecticidal metabolites (e.g. thiacloprid breaks down into clothianidin); and some imidacloprid metabolites that are common to other neonicotinoids, are also toxic to various life forms. Commonalities in their persistence, mechanisms of action and breakdown products argue that none would be a good substitute for another.

The Parliamentary Standing Committee on Agriculture and Agri-Food held a hearing March 9, 2017 regarding imidacloprid, at which it was stated by Pierre Giovenazzo, Professor, Sciences apicoles, Centre de recherche en sciences animales de Deschambault, Université Laval, that Canada has not been self-sufficient in bees since 2011. Packets containing queen bees must be imported annually. This potentially disastrous trend merits strong, prompt actions, particularly when the persistence of the implicated pesticides renders environmental and pollinator recovery a long-term proposition. To many Canadians, this fact, along with extensive research linking pollinator decline to persistent systemic insecticides,[1,2,3] should be sufficient to spur strong actions.

Substitution

The current proposal is to phase out one of six neonicotinoid-like insecticides currently registered in Canada (Table 1). When one chemical is phased out, a crucial consideration is what will be used in its place. Canada has a sorry history of banning well-known toxicants when they have reached excessive concentrations in an environmental compartment (in this case surface waters), but permitting similar chemicals to be substituted. There are no gains in environmental quality or public health, and the net result may only be that chemical companies are enriched when older, more commonly available chemicals are off the market and more expensive options are substituted. Some examples of unfortunate substitutions under the purview of Health Canada and inaction in the face of hazardous unnecessary products (albeit not the PMRA), include:

- bisphenol-A was banned from infants' products (but not from other sources of exposures in plastics and fragranced products), whereas common bisphenol substitutes can be just as estrogenic;[4]
- a succession of persistent, endocrine disrupting flame retardants have been permitted, and then banned once environmental levels reached unacceptable levels;[5] and
- endocrine disrupting chemicals such as antimicrobials triclosan and triclocarban; ultraviolet light absorbing organic sunscreen ingredients; and phthalates in diverse plastics, and cosmetics and other scented products, as described in our submission regarding the Canadian Environmental Protection Act (pp 16-18).[6]

Next steps, also discussed in the Parliamentary Standing Committee on Agriculture and Agri-Food hearing

With Canadian pollinators hanging in the balance, now is the time to break this treadmill, to act on the entire family of persistent systemic pesticides, and to reassess approaches to pest control in agriculture.

More sustainable agriculture is necessary to feed the world, according to two just-released reports, the European Parliamentary Research Service report, "Human health implications of organic food and organic agriculture" [7] and the United Nations Report of the Special Rapporteur on the right to food.[8] These reports highlight that current national regulations are not protecting human health and the environment from hazardous pesticides, that these pesticides have not, overall, reduced crop losses in the long term, and that these chemicals threaten the water and soil, biodiversity, pollinators and human health. Organic agriculture results in foods with higher nutrient content, lower levels of the highly toxic carcinogen cadmium in grains, and of course lower pesticide residues.[9] The United Nations Rapporteur states that human rights to adequate food and health are not met with the use of hazardous pesticides in agriculture.

Neonicotinoids have broad impacts on insect life, both directly and as the chemicals are transmitted through the food chain (at different "trophic levels"). A research study demonstrated that soy yields were decreased with neonicotinoid applications because the insecticide residues in the slugs killed predatory beetles.[10] This observation was generalized to arthropod predators and parasitoids, in a recent meta-analysis of over 1000 observations of abundance of natural enemies associated with and without neonicotinoid seed coats.[11]

Scientific review and human health

The scientific review of imidacloprid is lacking much of the relevant peer-reviewed literature. Beyond limitations of the ecological referencing noted above, a series of reports of human intoxication from the Japanese group lead by Dr. Kumiko Taira, are all missing from the consultation document. Health Canada, and the PMRA in particular, should carry out international best practices in systematic scientific review, so that the present claims of "weight of evidence" are transparently supported with the scientific evidence systematically presented along with meta-analyses when appropriate, grading of said evidence, and final weighing.[12]

Final breakdown products of chloropyridine-containing insecticides

As illustrated in Table 1, four insecticides contain the 2-chloropyridine (2CP) moiety. All are noted to break down to 6-chloronicotinic acid (6CA). There is the concern that as indicated by Bayer (Attachment 1), the indicated loss of carbon dioxide from 6CA results in 2CP. We brought this up with regard to flupyradifurone, and the PMRA responded as follows:[13]

> *PMRA can confirm that several aerobic soil studies were conducted with the pyridine ring labelled flupyradifurone and 2-chloroypridine was not observed. Furthermore, although a number of group 4 insecticides (including flupyradifurone and imidacloprid) contain 2-chloropyridine in their molecular structures, an internal database search showed that none of these chemicals produced 2-chloropyridine in chemical and biological transformation studies. A search of available literature yielded no additional information regarding 2-chloropyridine being produced as a transformation product of any insecticide. Based on inspections of the chemical structure and the proposed transformation pathways of flupyradifurone, the most probable precursor to form 2-chloropyridine would be decarboxylation of 6-chloronicotinc acid (6-CNA). However, a submitted study conducted with 14C labelled 6-CNA (labelled at 2 and 6 positions of the pyridine ring) showed that 6-CNA transformed rapidly in aerobic soils, forming 14CO2 (84-92% AR), non-extractable residues (9.7-14.5% AR) and two unknown components (at maximum of 3 and 5% AR, respectively). These results do not suggest the formation of 2-chloropyridine. The formation of 14CO2 is indicative of pyridine ring fission. The transient nature of the two unknowns (non-detectable within 14-31 days) suggests that they are not likely to be 2-chloropyridine, as it is understood to be persistent. Finally, 2-chloropyridine is highly soluble in water (25 g/L at 25°C) and alcohol, and thus, if it were formed, it would be detected in the ammonium acetate/methanol (20:80 v/v) extracts. Therefore, at the present time, Health Canada has no evidence to suggest that 2-chloropyridine is a breakdown product of flupyradifurone.*

In this regard, we make the following observations:

- There is no indication that 2CP was actively investigated using spiked samples; merely that it was not observed. Experience gained at the University of Toronto during development of an analytical method to measure 2CP indicates that this chemical does not stay in aqueous solution. 2CP is prone to volatilizing. Lack of an observation of 2CP can in no way be conclusive, as it is likely to be escaping into the air under experimental conditions, and without confirmation of chemical identities, radioactivity in the vapour phase may have been 2CP. Therefore, a conclusion should not be reached regarding the presence or absence of 2CP unless experimental methods thoroughly investigate this specific possibility.
- The rapid transformation of 6CNA in the noted but unreferenced study was possibly with a bacterium that was isolated from enrichment cultures, reported in the literature.[14] This research merely reported mineralization, and detection of a dechlorination product of 6CNA. According to Dr. Carolyn Cummins at the University of Toronto, who is working on 2CP, she was unsuccessful at detecting 2CP using a method similar to that described in the referenced paper because the 2CP is not adequately retained on that type of column. Again, this research does not prove an absence of 2CP.

In conclusion, we continue to be very concerned despite the discussion put forward by the PMRA with regard to environmental degradation of 6CNA. If anything, the lack of thorough, sound scientific investigation over a decade of highlighting this issue heightens concerns. We are also frustrated by being told that we cannot view information in the Reading Room as long as it is pertinent to a pesticide that is under review. Since imidacloprid has been under review for over 20 years, this information has not been available to the public view.

In conclusion, PCN supports the phase-out of imidacloprid, and all other systemic insecticides. In this situation, equally harmful substitutions are highly likely, with no health or environmental benefits apparent from removing only one of the six chemicals indicated in Table 1.

Given that:

- Canada has had to import bees since 2011;
- the strong evidence linking persistent systemic insecticides with pollinator decline; and
- the fact that bioeffects are not quickly reversed when persistent chemicals are involved,

it is not an understatement to say that this is a critical issue of food security. The national government would be wise to follow the example of Quebec, and the advice of the United Nations Rapporteur and many others before, to shift gears to rapidly build expertise and capacity in organic agriculture.

Finally, the PMRA must improve its searching, review and scrutiny both of the scientific literature and chemistry for use in its evaluation and re-evaluation of pesticides.

Sincerely,

Meg Sears PhD
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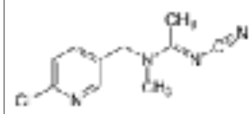
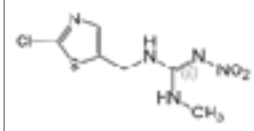
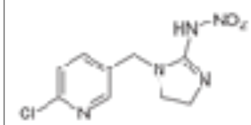
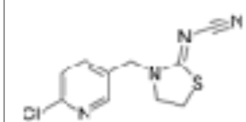
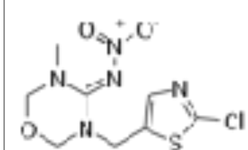
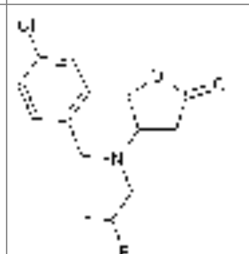
Table 1. Canadian-Registered Neonicotinoid-like Insecticides. 2-chloropyridine moieties are encircled.

Neonicotinoid	Labels registered on PMRA Label Search	Uses	Structure
Acetamiprid	4 labels – Nippon Soda Company	Seed treatment, flowable, granules	
Clothianidin	16 labels – Bayer, Valent, Syngenta *NOTE: Clothianidin is a metabolite of Thiamethoxam*	Seed treatments; cockroach bait + indoors; granular; mixtures with other insecticides or fungicides	
Imidacloprid	91 labels	Indoor, outdoor, seed treatments, tree injection, crop, flea&tick&lice products for pets; mixtures	
Thiacloprid	1 label for Calypso; Bayer Cropscience	For pome fruit	
Thiamethoxam	22 labels 21 Syngenta; 1 Elanco Many with other chemicals (e.g. Cruiser Vibrance Quattro has 5 active ingredients) http://pr-rp.hc-sc.gc.ca/1_1/view_label?p_ukid=81908642 *NOTE: Thiamethoxam breaks down into Clothianidin*	Seed treatments, flowable granules, wettable granules, fly bait, etc.	
Flupyradifurone	2 labels; Bayer Cropscience Inc.	Suspension or solution for fruit, vegetable and field crops	

Attachment 1

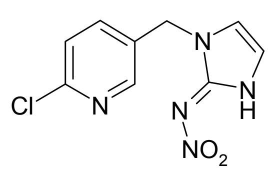
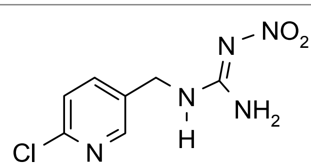
Note from PCN: this material is considered confidential data by the PMRA, but was provided to Ottawa City Council and thus entered the public record. This material is provided in its entirety, but of chief importance is the bottom of the breakdown pathway chart, depicting decarboxylation of 6-chloronicotinic acid. This would likely result in 2chloropyridine.

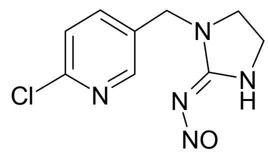
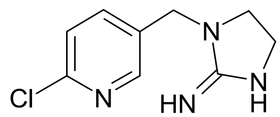
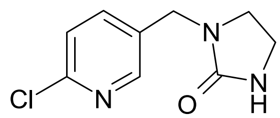
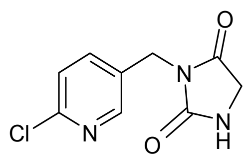
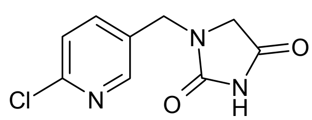
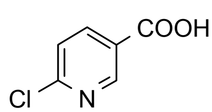
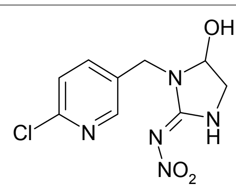
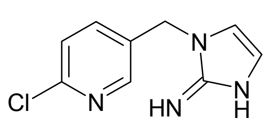
Soil Metabolism of Imidacloprid

Metabolism studies show that imidacloprid is thoroughly metabolized in soil, finally leading to the formation of carbon dioxide and portions of not extractable (bound) residues. By using a 14C labelled test substance it can be proven that bound residues of imidacloprid participate in the natural carbon cycle of soil. Transformation proceeds via several minor metabolites none representing more than 4% of the applied dose and most representing 2% of the applied dose. The absence of any major metabolite accounting for more than 4 % of the applied radioactivity indicates that the first reaction step determines the overall rate of degradation and complete mineralization. Subsequent degradation of the metabolites occurs more rapidly than that of the parent, and, therefore, significant residue levels of metabolites do not accumulate in soil at any time post treatment. From the results of the soil metabolism studies it can be concluded that imidacloprid is completely degradable. In order to determine the rate of degradation of total residues of imidacloprid in soil under outdoor field conditions it is adequate to monitor the decline of the parent compound concentration as a function of time.

The metabolites found in different soil degradation studies are listed in the table below. From the metabolites identified in these studies a metabolic pathway as given in the figure can be proposed.

List of metabolites found in soil degradation studies with imidacloprid

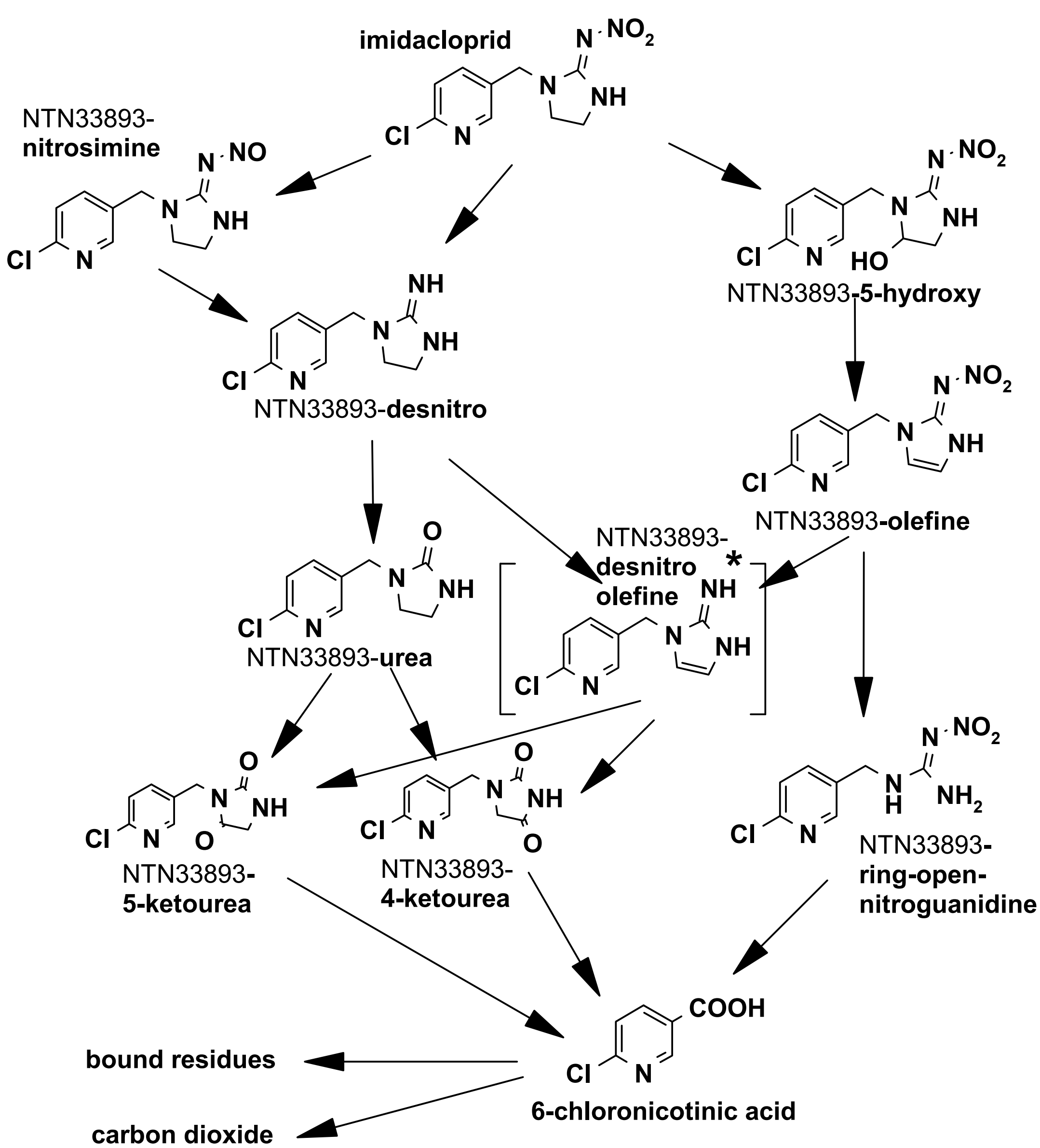
Name of Compound used in reports	Structural Formula	Maximum concentration in various studies
M06 NTN33893-olefine		1.8 % at day 100 [1)]
		1.1 % at day 274 [1)]
M11 NTN33893-ring-open-nitroguanidine		1.8 % at day 100 [2)]
		1.6 % at day 274 [2)]
		1.7 % at day 201
		1.0 % at day 366
		1.3 % at day 56

M07 NTN33893-nitrosimine		0.8 % at day 35
M09 NTN33893-desnitro (NTN33893-guanidine)		1.8 % at day 100 0.4 % at day 100 3.3 % at day 201
M12 NTN33893-urea		0.3 % at day 62 0.4 % at day 120
M33 NTN33893-5-keto-urea		1.8 % at day 100 [5)] 1.6 % at day 59 [5)]
M34 NTN33893-4-keto-urea		1.8 % at day 100 [4)] 1.1 % at day 274 [4)]
M14 NTN3393-6-CNA 6-chloronicotinic acid		1.0 % at day 56
M01 NTN33893-5-hydroxy		0.28 % at day 201
M23 NTN33893-desnitro-olefine		3)

Notes:
[1)]Value is the sum of NTN33893-4-keto-urea and N4TN33893-olefine as both components were not separated analytically from each other

2)Value is the sum of NTN33893-ring-open-nitro-guanidine and NTN33893-5-keto-urea as both components were not separated analytically from each other
3)Value is the sum of NTN33893-4-keto-urea and NTN33893-olefine as both components were not separated analytically from each other
4)Value is the sum of NTN33893-ring-open-nitro-guanidine and NTN33893-5-keto-urea as both components were not separated analytically from each other
5) [...] = proposed structure of postulated intermediates

Proposed metabolic pathway for aerobic degradation of Imidacloprid in soil



References

1. Simon-Delso, N. *et al.* Systemic insecticides (neonicotinoids and fipronil): trends, uses, mode of action and metabolites. *Environ. Sci. Pollut. Res. Int.* **22,** 5–34 (2015).
2. Lexmond, M. B. van, Bonmatin, J.-M., Goulson, D. & Noome, D. A. Worldwide integrated assessment on systemic pesticides. *Environ. Sci. Pollut. Res.* **22,** 1–4 (2015).
3. Sluijs, J. P. van der *et al.* Conclusions of the Worldwide Integrated Assessment on the risks of neonicotinoids and fipronil to biodiversity and ecosystem functioning. *Environ. Sci. Pollut. Res.* **22,** 148–154 (2015).
4. Mesnage, R. *et al.* Transcriptome profiling reveals bisphenol A alternatives activate estrogen receptor alpha in human breast cancer cells. *bioRxiv* (2017). doi:10.1101/112862
5. Prevent Cancer Now & Chemical Sensitivities Manitoba. Response to Environment and Climate Change Canada consultation: Certain Organic Flame Retardant Substances. (2016).
6. Prevent Cancer Now, Chemical Sensitivities Manitoba & National Network on Environments and Women's Health. Submission to the Standing Committee on Environment and Sustainable Development Re.Canadian Environmental Protection Act (CEPA) Review Controlling Toxic Substances. (2016).
7. European Parliamentary Research Service. Scientific Foresight Unit (STOA). Human health implications of organic food and organic agriculture. (2016).
8. Human Rights Council, United Nations. Report of the Special Rapporteur on the right to food. (2017).
9. Barański, M. *et al.* Higher antioxidant and lower cadmium concentrations and lower incidence of pesticide residues in organically grown crops: a systematic literature review and meta-analyses. *Br. J. Nutr.* **112,** 794–811 (2014).
10. Douglas, M. R., Rohr, J. R. & Tooker, J. F. Neonicotinoid insecticide travels through a soil food chain, disrupting biological control of non-target pests and decreasing soya bean yield. *J. Appl. Ecol.* **52,** 250–260 (2015).
11. Douglas, M. R. & Tooker, J. F. Meta-analysis reveals that seed-applied neonicotinoids and pyrethroids have similar negative effects on abundance of arthropod natural enemies. *PeerJ* **4,** (2016).
12. Rooney, A. A., Boyles, A. L., Wolfe, M. S., Bucher, J. R. & Thayer, K. A. Systematic Review and Evidence Integration for Literature-Based Environmental Health Science Assessments. *Environ. Health Perspect.* **122,** 711–718 (2014).
13. Health Canada, Pest Management Regulatory Agency, Government of Canada. Registration Decision: Flupyradifurone (RD2015-24, November 25, 2015). (2015). Available at: http://www.hc-sc.gc.ca/cps-spc/pubs/pest/_decisions/rd2015-24/index-eng.php#a1. (Accessed: 20th March 2017)

14. Shettigar, M. *et al.* Cloning of a Novel 6-Chloronicotinic Acid Chlorohydrolase from the Newly Isolated 6-Chloronicotinic Acid Mineralizing Bradyrhizobiaceae Strain SG-6C. *PLOS ONE* **7,** e51162 (2012).