PREVENT CANCER NOW

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Submission to
Health Canada, Pest Management Regulatory Agency
regarding
Proposed Registration Decision PRD2014-20
Flupyradifurone

Prevent Cancer Now (PCN; www.preventcancernow.ca) is a national Canadian organization working to eliminate preventable causes of cancer. PCN provides public education, as well as input, including to governmental consultations. PCN scientists and medical experts provide information, based on broad understanding of the science of contributors to cancer. PCN also recognizes that contributors to the development of cancer also affect prevalence of other chronic diseases.

PCN opposes the registration of flupyradifurone because of anticipated effects on pollinators, use of low margins when extrapolating from effects in animals to vulnerable humans, and inadequate identification and assessment of breakdown products. A very persistent, possibly carcinogenic breakdown product, 2-chloropyridine, was omitted entirely be abbreviating the assessment. Examination of 2-chloropyridine in the environment merits urgent action.

PCN opposes the registration of flupyradifurone because
according to the assessment document PRD2014-20:

- Flupyradifurone is persistent, and eventually breaks down into other toxic, persistent chemicals.
- Flupyradifurone acts on the same nicotinic acetylcholine receptors as neonicotinoid insecticides. These chemicals are currently banned in Europe to protect pollinators. Additives and synergistic effects with existing environmental pesticides and breakdown products were not considered.
- Pollinators would be expected to be adversely impacted by this persistent insecticide. Although studies on bees (*Apis*) were listed, unlike effects on other organisms like earthworms, no results were presented. Killing insect pests may boost one crop one year; undermining pollinators undermines our entire food system.
- A target margin of effect (MoE) of 100 was used for this assessment. This is a low value, and is not consistent with requirements under the Pest Control Products Act (2002) for an additional extrapolation factor to protect vulnerable population. Proposals to use this low MoE was opposed by the Ontario College of Family Physicians Environmental Health Committee and other scientists during consultation on implementation of the PCPA on many grounds, including that it does not encompass inter-individual variability, and that it ignores the intention of the new Act.
- Additionally, rather than "no observed effect levels" the MoE was applied to "no observed *adverse* effect levels." Under this paradigm, effects that would be concerning, for instance for parents (e.g. lower activity levels or watery eyes), are not considered "adverse," and permitted pesticide exposures are inflated. This approach combined with a low MoE permits higher residues than otherwise, and thereby higher application rates. Proposed allowable residues are particularly high for leafy greens – foods that are encouraged for a healthy diet.

At least as importantly, PCN opposes the registration of flupyradifurone because of ***what is omitted from the assessment document***:

- Although flupyradifurone is classified as somewhat different from neonicotinoids, they all not only interact with* the same nicotinic acetylcholine receptors, many also share the cloropyridyl group (see Attachment 1).
- As seen in assessments of neonicotinoid insecticides, examination of flupyradifurone environmental degradation information was abbreviated at formation of 6-chloronicotinic acid (6CNA). The next breakdown step for 6CNA, indicated in Bayer's information regarding imidacloprid (Attachment 2), will be decarboxylation. This reaction creates 2-chloropyridine (also called o-chloropyridine, or sometimes incorrectly 6-chloropyridine).
- We were unable to locate information directly regarding 2-chloropyridine and flupyradifurone, and 2-chloropyridine is not mentioned in the PMRA assessment document; however, 2-chloropyridine is formed via 6CNA, which is a degradation product also of the neonicotinoid insecticides imidacloprid, acetamiprid and thiocloprid.
- Breakdown to 2-chloropyridine was not captured in the radiolabelling studies because the pyridine ring was not labeled. (PRD2014-20, p 75/PDF p 81). Neither has the toxicity of 2-chloropyridine been incorporated into considerations regarding the pesticides with this common breakdown product.
- Previous queries to the PMRA, regarding monitoring for 2-chloropyridine have not yielded data. It has been assessed in neither environmental nor biological systems, to the best of our knowledge. *Environmental and biological levels of 2-chloropyridine is an important data gap that should be filled urgently.*
- Persistence of flupyradifurone and selected breakdown products, on foods and in the environment is confirmed within PRD2014-20. According to assessments reported by the European Chemicals Agency (www.echa.eu)[1] no environmental breakdown of 2-chloropyridine was observed under test conditions. The US Environmental Protection Agency similarly indicates environmental persistence of 2-chloropyridine.[2]
- The above authorities also indicate that *2-chloropyridine has the characteristics of a carcinogen.* Mutagenicity tests are positive, particularly with metabolic activation. 2-chloropyridine is very irritating, and extremely toxic to the liver.

Respectfully submitted,

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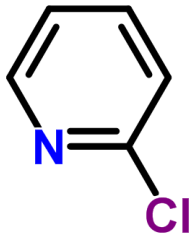
References

1. European Chemicals Agency. 2-chloropyridine [Internet]. [cited 2014 Oct 17]. Available from: http://apps.echa.europa.eu/registered/data/dossiers/DISS-9c8013db-b63d-4d13-e044-00144f67d249/AGGR-229ae07a-dc0d-4fbe-a512-d136f0e51b34_DISS-9c8013db-b63d-4d13-e044-00144f67d249.html#AGGR-229ae07a-dc0d-4fbe-a512-d136f0e51b34

2. Arch Chemicals Inc. High Production Volume (HPV) Challenge Program Test Plan for 2-chloropyridine [Internet]. 2003. Available from: http://www.epa.gov/HPV/pubs/summaries/2chlorop/c14277.pdf

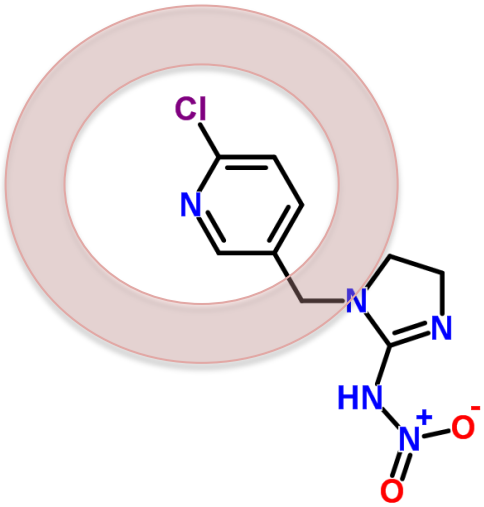
* corrected – original version incorrectly stated "blocked." The pesticides activate the receptors.

Attachment 1

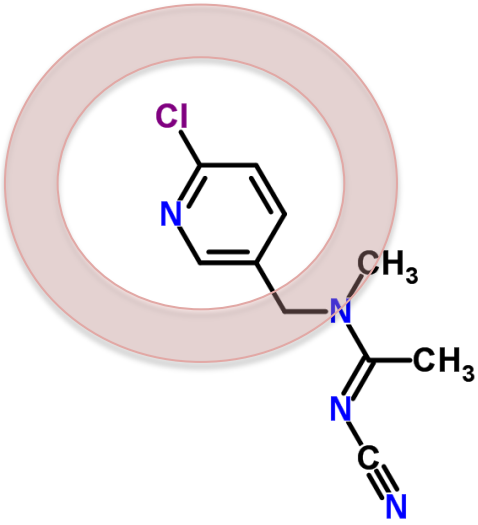


2-chloropyridine is a common breakdown product of many neonicotinoid pesticides, as well as flupyradifurone

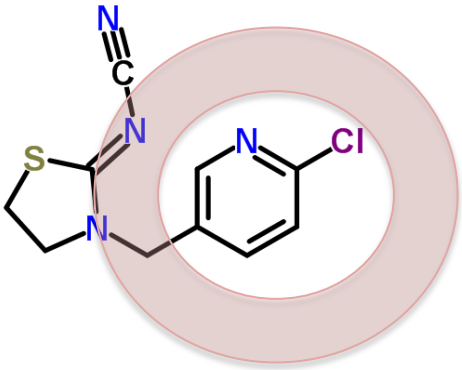
2-chloropyridine is very persistent in the environment and is reasonably expected to be a carcinogen (among other toxic effects)



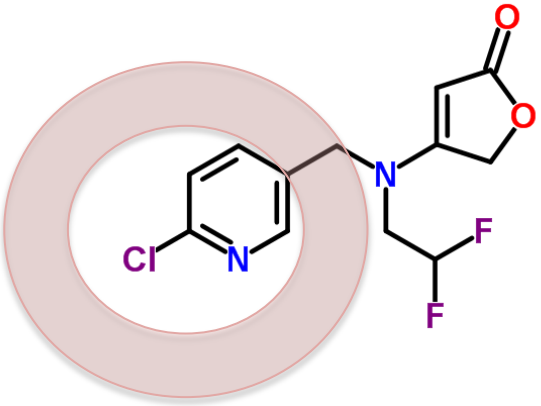
Imidacloprid – neonicotinoid



Acetamipride - neonicotinoid



Thiacloprid - neonicotinoid



Flupyradifurone

Attachment 2

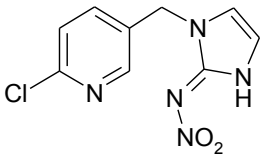
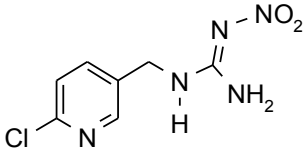
Note from PCN: this material is considered confidential data by the PMRA, but was provided to Ottawa City Council and thus entered the public record. This material is provided in its entirety, but of chief importance is the bottom of the breakdown pathway chart, depicting decarboxylation of 6-chloronicotinic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

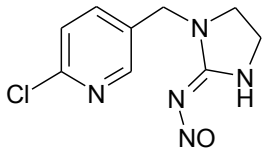
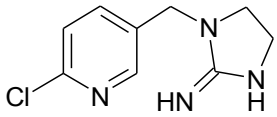
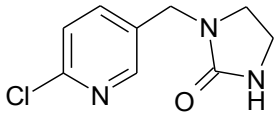
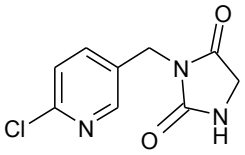
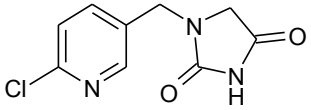
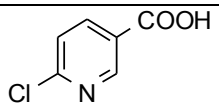
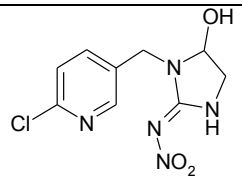
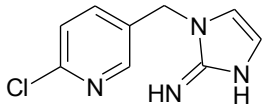
Soil Metabolism of Imidacloprid

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