HHS Public Access

Author manuscript

Environ Sci Technol. Author manuscript; available in PMC 2023 May 01.

Published in final edited form as:

Environ Sci Technol. 2021 February 02; 55(3): 2163–2164. doi:10.1021/acs.est.0c03723.

Comment on "Urinary Metabolites of Neonicotinoid Insecticides: Levels and Recommendations for Future Biomonitoring Studies in China": Quantification of 5-Hydroxyimidacloprid and Biomonitoring

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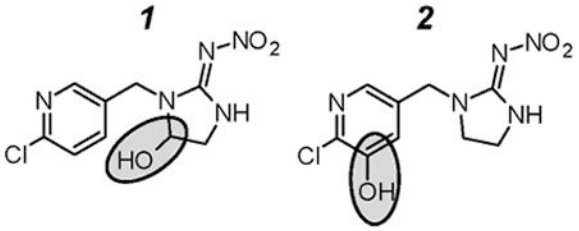
We recently read the article of Song et al. on human biomonitoring of urinary metabolites of neonicotinoids with high interest.[1] Our own experiments[2] on the metabolism of imidacloprid after a single oral dose of 5 mg in a male volunteer do confirm the findings of Song and co-workers that 5-hydroxyimidacloprid (5-OH-IMI) and imidacloprid olefin are relevant metabolites of imidacloprid in humans. Unfortunately, the article, like several others, has a serious shortcoming from an analytical point of view.

The metabolism of imidacloprid has previously been described in sufficient detail in mammals;[3,4] whereas data in humans are scarce and mostly qualitative.[5] Available studies indicate that 5-OH-IMI is a major specific metabolite of imidacloprid; however, not just any 5-OH-IMI but one that is hydroxylated at the 1H-imidazol moiety (***1***, CAS no. 155802–61–2). Therefore, using the correct 5-OH-IMI standard material for chemical analyses for human biomonitoring of imidacloprid is a critical first step. For example, in preparation for our controlled studies in humans, we had to synthesize ***1*** and a $^{13}C_2$, ^{15}N isotope labeled analogue because the substances were not commercially available at that time.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the CDC. Use of trade names is for identification only and does not imply endorsement by the CDC, the Public Health Service, or the US Department of Health and Human Services.

The authors declare no competing financial interest.



Meanwhile, because of increased public interest in neonicotinoids, commercial suppliers of standard materials started to offer 5-OH-IMI. Unfortunately, two different forms of 5-OH-IMI with identical molecular masses are commercially available. In addition to ***1***, there is a second 5-OH-IMI hydroxylated at the 6-chloro-3-pyridinyl moiety (***2***, CAS no. 380912–09–4) and not known to be a metabolite of imidacloprid. Interestingly, ***2*** is also commercially available under a very similar name, i.e., "5-hydro-imidacloprid." Therefore, without specifically asking the supplier for structural information and proof of authenticity, it is possible to end up with the wrong standard for analytical method development.

In our opinion, this is what, unfortunately, happened to Song and co-workers. They reported that they obtained their 5-OH-IMI standard from Ehrenstorfer GmbH, Germany, a company that partially sources its substances from third parties. However, Ehrenstorfer does not offer ***1***, only ***2*** (under the name "5-hydro-imidacloprid") purchased from TRC Chemicals, Toronto, Canada. Therefore, we believe Song and co-workers used the wrong 5-OH-IMI for standardizing their analytical method even though they showed the correct chemical structure of ***1*** in the TOC picture on the front page of their article.

To the best of our knowledge, with the exception of Baker et al.[6] and Ospina et al.[7] other researchers who have claimed to quantify 5-OH-IMI as a metabolite of imidacloprid in humans also used ***2*** instead of ***1***.[8-10] Because of the structural similarities and identical molecular masses, both forms of 5-OH-IMI can have similar retention times and even similar precursor and product ion masses in mass spectrometry[6] and require authenticated standard material of ***1*** (e.g., IDM, Teltow, Germany).

Of note, Song and co-workers[1] may not be all that wrong with their concentrations determined in urine because of these similarities. Nevertheless, this issue can't simply be dismissed as a "technicality" because, in the end, exposure assessment by human biomonitoring relies on correctly standardized and validated analytical methods. Additionally, to choose the appropriate biomarkers and sampling times, basic toxicokinetic and quantitative data (i.e., urinary excretion fractions, elimination half-lives) are needed before proposing recommendations for human biomonitoring.

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