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Increasing use of pyrethroids in Canadian households: should we be concerned?

Running title: increasing household use of pyrethroids

Authors:

Erna C. van Balen*, MSc, MPhil. National Collaborating Centre for Environmental Health, Vancouver, Canada.

Marcelo J. Wolansky*, PhD. University of Buenos Aires, Autonomous City of Buenos Aires, Argentina.

Tom Kosatsky, MD, MPH. British Columbia Centre for Disease Control and National Collaborating Centre for Environmental Health, Vancouver, Canada.

*ECVB and MJW have an equal contribution to this work

Conflict of Interest

The authors have no conflicts of interest to declare.

Abstract

Pyrethroids are a class of plant-derived insecticides and their man-made analogues increasingly applied in Canada as first-choice for pest control in many agricultural and residential settings. Their popularity is partly due to their alleged safety compared to the older organochlorine and organophosphate insecticides. Application of pyrethroids is expanding because of recent increases in the level of pest infestations, such as by bed bugs, and due to decreased susceptibility of target species to many pest control products. Pyrethroid residues have been documented in homes, child care centers and food. While pyrethroids are considered of low health risk for humans, their increased use is of concern. Our current understanding of the adverse effects of pyrethroids derives mainly from studies of short-term effects in laboratory animals, case reports of self and accidental poisonings, and high-dose occupational exposures, for which levels and formulations of pyrethroid products differ from long-term exposure in the general population. The available data suggest that the reproductive and nervous systems, endocrine signalling pathways and early childhood development may be targets for adverse effects given repeated exposure to pyrethroid formulations. Given uncertainty about the existence of long-term health effects of exposure to pyrethroids among multiple stressors, particularly under realistic, scenarios, we should be cautious when promoting pyrethroid products as safe methods for pest control.

MeSH terms: Pyrethrins, Environmental Exposure, Endocrine Disrupting Chemicals, Toxicology, Risk Assessment

Introduction

Pyrethroid insecticides and naturally occurring pyrethrins are commonly used for insect control in households and in agriculture.[1] Reasons for this are increasing restrictions in the use of organophosphate and organochlorine insecticides, the greater selectivity of pyrethroids for certain target species,[2] their moderate acute oral toxicity in vertebrates and humans,[3] and relatively low levels of environmental residues due to rapid degradation outdoors.[1] While pyrethroids have received both scientific[2] and regulatory[4,5] attention, questions remain as to their safety, especially for residential applications.

What are pyrethroids?

Natural pyrethrins are present in pyrethrum extracts obtained from flowers of some species of chrysanthemum. Because pyrethrins degrade easily under the influence of water and sunlight, more stable alternatives, the synthetic pyrethroids, have been developed, allowing for longer intervals between applications.[1] Pyrethroids and pyrethrins act on the nervous system of flying insects by disrupting the function of sodium channels. They delay the closing of these channels, which results in repetitive firing of neurons, causing paralysis and death.[1,2] Pyrethroids produce toxicity in non-target species such as mammals in a similar manner.[1,6,7]

Synthetic pyrethroids are generally classified into two types, based on toxicological and physical-chemical properties. “Type-I”-like pyrethroids include allethrin, bifenthrin, permethrin, phenothrin, resmethrin, tefluthrin and tetramethrin. Examples of “Type-II” pyrethroids are cyfluthrin, cyhalothrin, cypermethrin and deltamethrin.[1] In Canada, the natural pyrethrins and the synthetic pyrethroids permethrin, allethrin, tetramethrin, phenothrin and resmethrin are registered for residential use.[8] More than 600 of 2144 pesticide products currently registered for residential pest control in Canada contain one or more of these substances.[8]

In humans, pyrethroids are rapidly metabolized and excreted in urine. The identification of primary metabolites in urine is of little utility in distinguishing exposure to specific pyrethroids: metabolic pathways for different parent compounds produce the same breakdown products. For example, 3-phenoxybenzoic acid (3-PBA) is a common metabolite of cyhalothrin, cypermethrin, deltamethrin, fenpropathrin, permethrin and tralomethrin. The *cis* and *trans* configurations of 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid (i.e., *cis*-DCCA and *trans*-DCCA) are the metabolic products of the *cis* and *trans* isomers of cypermethrin, cyfluthrin or permethrin, respectively.[1] Thus, the specific pyrethroid to which an individual was exposed, and its source (e.g. diet or residential use) cannot be readily determined only by analyzing urine.[9]

To what degree are pyrethroids used?

To the best of our knowledge, there are no Canadian residential use data. In the U.S., 2 million pounds of permethrin, the most common pyrethroid used, are applied annually in agricultural and residential settings. The majority of permethrin, over 70%, is applied in non-agricultural settings.[10] Again in the U.S., permethrin residues were found in 89% of homes in a representative sample in 2005-2006.[11] In general, pyrethroids registered for home pest control are assumed to degrade rapidly in the environment under the influence of water and sunlight, thus limiting the potential for household exposure. However, when applied indoors, they may not degrade as rapidly and possibly accumulate in homes, creating a potential for repeated and long-term exposure through contact with floors and other surfaces.

How toxic are pyrethroids?

Structural differences between pyrethroid compounds result in large variations in toxicity (as expressed in acute toxicity experimentation in small rodents).[1,6,7] There are also other determinants of toxicity in mammals. For instance, formulated commercial products may differ in toxicity from technical grade products, and the toxicological profile of the formulated product is not necessarily identical to that of the pure active ingredient. The ratio of *cis* and *trans* configurations in commercial products is also an important determinant of pyrethroid toxicity in mammals, with *cis* isomers generally being more potent.[1,12] Finally, commercial pest control products contain up to 99% of “inert” ingredients, such as synergists (piperonyl butoxide, sulfoxide, sesamex) and solvents. They are relatively non-toxic chemicals, but co-administered in sufficient amounts with active ingredients, they can decrease the threshold doses for pyrethroid toxicity in humans.[1]

We have little knowledge of long-term effects

Effects of acute exposure to high levels of pyrethroids are well-known and documented. In general, chemicals are tested at high-effective doses and safe levels are established based on the lowest observed adverse effect level (LOAEL) or the no observed adverse effect level (NOAEL) estimates obtained from examining a few endpoint in animals. Then, safety factors are used to extrapolate from laboratory animals to humans. However, this approach may not be appropriate, as post-marketing surveillance has shown adverse effects at levels of exposure considered non-toxic at the time of chemical registration. Further, present assumptions of the safety of long-term exposures in humans are not based on empirical assessments using realistic scenarios of repeated low-dose uptake of multiple pyrethroid compounds. Concerns for effects of long-term exposure include endocrine disruption,[2,13] functional alterations at reproductive organs,[2,13] and effects on neurologic development.[7,14]

Based on the potential for exposure through three of the four exposure pathways, the U.S. Environmental Protection Agency has included permethrin on its list of chemicals to be screened for their effects on the endocrine system.[15] Endocrine disruption is of great importance because chemicals targeting endocrinological domains can have effects at low doses that are not predicted by effects at higher doses.[16]

Both animal studies and studies in non-occupationally exposed humans indicate that pyrethroid exposure can affect sperm concentration, motility and morphology. For example, significant positive associations were found between pyrethroid metabolites in urine and FSH and LH levels in serum in non-occupationally exposed men.[2] Elevated levels of FSH are highly predictive of poor semen quality. Associations were also found between sperm quality parameters (concentration, motility, sperm DNA damage and DNA fragmentation) and pyrethroid metabolites in urine.[2,13] Although study subjects were recruited from infertility clinics, men with the highest levels of pyrethroid metabolites in their urine had lower semen quality, higher levels of sperm DNA damage and higher levels of DNA fragmentation.[2]

Since pyrethroids primarily act on the nervous system of insects and mammals[14] there is also concern for neurological and neuropsychological effects of pyrethroid exposure, such as effects on behaviour, learning and motor performance.[7] So far, this has only been studied in small rodents. Preliminary evidence indicates that there are age-related differences in neurotoxicity, with lactating rat pups being up to one order of magnitude more sensitive to the acute effects of deltamethrin, cypermethrin and permethrin than adult animals when middle-to-high effective doses are administered by the oral route:[14] this may have important implications for the safety of pyrethroids in babies and small children.

Combined exposure to pyrethroids and other chemicals is relevant to realistic exposure scenarios. The effects of repeated exposure to multiple pyrethroids at environmentally relevant levels may differ qualitatively and quantitatively from the acute or subacute effects of clinically effective doses of single compounds. For example, a recent study of the combined action of eleven pyrethroids on motor activity in rats demonstrates that sub-effective levels of the individual test chemicals may become toxic when co-administered in laboratory animals.[17] Also, there is limited evidence that combined administration of pyrethroids with insect repellents such as DEET and some organophosphates might have additive or synergistic effects on the nervous system.[1]

Why should we be concerned?

There are several reasons to be concerned about pyrethroids. First, household use of pyrethroid appears to be common: 89% of U.S. homes had detectable levels of permethrin.[11] Although 15% of Canadian households are reported to use pesticide products indoors,[18] no Canadian data are available on the presence of pyrethroid residues in homes. Pyrethroids are the active ingredients of many insecticidal products, including sprays, pet shampoos against ticks and lice, foams, mosquito coils, and powders that appear to be ubiquitous in households. For example, permethrin is used to control bed bugs; its widespread use has likely contributed to the recently documented greater resistance of bed bugs and subsequent increase in infestation rates.[19] It has been shown that pyrethroids rank at the top of the list of most used active ingredients in insecticide products, and that this may result in health effects: in a recent U.S. study, pyrethroids, pyrethrins, or both were implicated in 89% of illnesses from insecticides used to control bed bugs.[20]

Second, pyrethroids do not remain in the air but deposit onto surfaces and may accumulate in house dust[21] due to their low vapour pressure.[1] They may not degrade as rapidly in indoor environments as previously thought. It has been stated that household exposure contributes little to the overall uptake of pyrethroids, and that diet is the most significant source of the body burden.[1] Recent research shows that household use may actually contribute more to overall pyrethroid exposure than diet, especially for small children (who crawl on the floor and practice hand-to-mouth behaviour).[9,22] Multi-day measurements strongly suggest that the variation in levels of pyrethroid metabolites can be attributed to pest control product applications at home,[9,23] and that peaks following household use of insecticide products may be more relevant for long-term health risks than food consumption, especially when exaggerated or improper application is practiced.

Pyrethroids are assumed to be rapidly metabolized in mammals, but a recent study shows that pyrethroids bioaccumulate in dolphins and are transferred from mother to calf through breast milk.[24] A body burden of pyrethroids has also been found in humans: metabolite levels found in urine samples in the Canadian population are of similar levels to those observed in the U.S. population.[25,26] Although measurable levels of pyrethroid metabolites do not necessarily mean that adverse health effects will occur,[3] the fact that they are detected in the general population indicates that the alleged high metabolic capacity for pyrethroids in mammals, including humans, may not be optimal and that exposure is likely to be ongoing.

Implications for public health

No reliable data on use and exposure are available for Canada, but public health professionals should be aware that pyrethroids are almost certainly ubiquitous in Canadian households. Education is needed because occupants may not realize that many of the products they use contain pyrethroids.

Public health practitioners may also help lobby for better labelling of pyrethroid products. For example, information on the ratio of *cis* and *trans* isomers, which greatly affects toxicity, is often not included on Material Safety Data Sheets. Also, it is known that people often do not understand the technical information and application instructions included on pesticide labels,[27] which may result in improper use and sometimes higher application rates than those recommended on the label.[28]

Pyrethroids may be perceived as safe because they are wrongly thought to be “natural”. People may equate natural pyrethrins and synthetic pyrethroids, and deem both natural and safe. Modern synthetic pyrethroids are certainly not natural, but man-made chemicals that were designed to optimize the insecticidal attributes of natural pyrethrins. Further, natural does not necessarily mean harmless.

A handful of reports unequivocally indicate that exposure to pyrethroids may lead to alterations in the neurological, endocrine and reproductive domains at doses near and below previously proposed toxic thresholds in laboratory animals. It is presently unclear to what extent these findings can be extrapolated to humans. Few human studies are available, but preliminary results seem to point in the same direction.[2,13] At present, empirical evidence is lacking to produce well-informed decisions on health protection from long-term exposure to pyrethroid insecticides.

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References

1. Todd GD, Wohlers D, Citra M. Toxicological profile for pyrethrins and pyrethroids. Atlanta, GA: Agency for Toxic Substances and Disease Registry, Centers for Disease Control and Prevention; 2003 Sep. Available from: http://www.atsdr.cdc.gov/ToxProfiles/tp.asp?id=787&tid=153.
2. Koureas M, Tsakalof A, Tsatsakis A, Hadjichristodoulou C. Systematic review of biomonitoring studies to determine the association between exposure to organophosphorus and pyrethroid insecticides and human health outcomes. Toxicol Lett. 2011 Apr 25;210(2):155-68.
3. Centers for Disease Control and Prevention. Fourth national report on human exposure to environmental chemicals 2009. Atlanta, GA: U.S. Department of Health and Human Services; 2009. Available from: http://www.cdc.gov/exposurereport/.

4. Health Canada. Re-evaluation note REV2011-05, re-evaluation of pyrethroids, pyrethrins and related active ingredients. Ottawa, ON: Health Canada; 2011 Dec. Available from: http://www.hc-sc.gc.ca/cps-spc/pubs/pest/_decisions/rev2011-05/index-eng.php.

5. U.S. Environmental Protection Agency. EPA's reevaluation of pyrethrins, pyrethroids and synergists. Washington, DC: EPA; 2012 [updated 2012 May 9; cited 2012 July 11]; Available from: http://www.epa.gov/oppsrrd1/reevaluation/pyrethroids-pyrethrins.html#epa.

6. Soderlund DM, Clark JM, Sheets LP, Mullin LS, Piccirillo VJ, Sargent D, et al. Mechanisms of pyrethroid neurotoxicity: implications for cumulative risk assessment. Toxicology. 2002;171(1):3.

7. Wolansky MJ, Harrill JA. Neurobehavioral toxicology of pyrethroid insecticides in adult animals: A critical review. Neurotoxicol Teratol. 2008;30(2):55-78.

8. Pest Management Regulatory Agency. Pesticide label search. Ottawa, ON: Health Canada; [updated Apr 17, 2012; cited 2010 Dec 20]; Available from: http://www.hc-sc.gc.ca/cps-spc/pest/registrant-titulaire/tools-outils/label-etiq-eng.php.

9. Lu CS, Barr DB, Pearson MA, Walker LA, Bravo R. The attribution of urban and suburban children's exposure to synthetic pyrethroid insecticides: a longitudinal assessment. J Expo Sci Environ Epidemiol. 2009 Jan;19(1):69-78.

10. U.S. Environmental Protection Agency. Permethrin facts. Washington, DC: EPA; 2009. Available from: http://www.epa.gov/pesticides/reregistration/permethrin/.

11. Stout DM, Bradham KD, Egeghy PP, Jones PA, Croghan CW, Ashley PA, et al. American healthy homes survey: A national study of residential pesticides measured from floor wipes. Environ Sci Technol. 2009 Jun;43(12):4294-300.

12. Wolansky MJ, Crofton KM, Romero DM, Tornero-Velez R. PS2109. Revisiting the impact of biological and experimental conditions of laboratory animal studies on estimations of risk of neurotoxicity by exposure to pesticides in humans: the pyrethroid case. 51st Annual Meeting and ToxExpo - Society of Toxicology Annual Conference; Mar 11-15; San Francisco, CA: Toxicologist 126 (1), Oxford University Press; 2012. p. 454.

13. Perry MJ. Effects of environmental and occupational pesticide exposure on human sperm: A systematic review. Hum Reprod Update. 2008 May-Jun;14(3):233-42.

14. Shafer TJ, Meyer DA, Crofton KM. Developmental neurotoxicity of pyrethroid insecticides: Critical review and future research needs. Environ Health Perspect. 2005;113(2):123-36.

15. U.S. Environmental Protection Agency. Endocrine disruptor screening program (EDSP). Washington, DC: EPA; 2012 [cited 2012 Jul 4]; Available from: http://www.epa.gov/endo/.

16. Vandenberg LN, Colborn T, Hayes TB, Heindel JJ, Jacobs DR, Lee D-H, et al. Hormones and endocrine-disrupting chemicals: Low-dose effects and nonmonotonic dose responses. Endocr Rev. 2012 Mar 14.

17. Wolansky MJ, Gennings C, DeVito MJ, Crofton KM. Evidence for dose-additive effects of pyrethroids on motor activity in rats. Environ Health Perspect. 2009 Oct;117(10):1563-70.

18. Statistics Canada. Households and the environment 2007. Ottawa, ON: Statistics Canada; 2009 Jul. Available from: http://www.statcan.gc.ca/pub/11-526-x/11-526-x2009001-eng.pdf.

19. Davies TG, Field LM, Williamson MS. The re-emergence of the bed bug as a nuisance pest: Implications of resistance to the pyrethroid insecticides. Med Vet Entomol. 2012 Jan 11.

20. Jacobson JB, Wheeler K, Hoffman R, Mitchell Y, Beckman J, Mehler L, et al. Acute illnesses associated with insecticides used to control bed bugs - seven states, 2003-2010. Centers for Disease Control and Prevention; 2011; Available from: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6037a1.htm?s_cid=mm6037a1_x.

21. Quirós-Alcalá L, Bradman A, Nishioka M, Harnly ME, Hubbard A, McKone TE, et al. Pesticides in house dust from urban and farmworker households in California: an observational measurement study. Environ Health. 2011;10:19-.

22. Tulve NS, Egeghy PP, Fortmann RC, Xue J, Evans J, Whitaker DA, et al. Methodologies for estimating cumulative human exposures to current-use pyrethroid pesticides. J Expo Sci Environ Epidemiol. 2011;21(3):317-27.
23. Lu CS, Barr DB, Pearson M, Bartell S, Bravo R. A longitudinal approach to assessing urban and suburban children's exposure to pyrethroid pesticides. Environ Health Perspect. 2006 Sep;114(9):1419-23.
24. Alonso MB, Feo ML, Corcellas C, Vidal LG, Bertozzi CP, Marigo J, et al. Pyrethroids: A new threat to marine mammals? Environ Int. 2012;47:99-106.
25. Fortin M-C, Bouchard M, Carrier G, Dumas P. Biological monitoring of exposure to pyrethrins and pyrethroids in a metropolitan population of the Province of Quebec, Canada. Environ Res. 2008;107(3):343-50.
26. Health Canada. Canadian health measures survey: Summary of the biomonitoring results and government actions. Ottawa, ON: Health Canada; 2010.
27. Grey CNB, Nieuwenhuijsen MJ, Golding J. The use and disposal of household pesticides. Environ Res. 2005;97(1):109-15.
28. Brimble S, Bacchus P, Caux PY. Pesticide utilization in Canada: A compilation of current sales and use data. Ottawa, ON: Environment Canada; 2005. Available from: http://publications.gc.ca/site/eng/283211/publication.html.