Toxicology Letters 340 (2021) 1–3

Contents lists available at ScienceDirect

Toxicology Letters

journal homepage: www.elsevier.com/locate/toxlet

Correspondence

Critique of the "Comment" etitled *"Pyrethroid exposure: Not so harmless after all"* by Demeneix et al. (2020) published in the lancet diabetes endocrinology

Keywords:
Comment
Insecticides
Pyrethrins
Environmental exposure
Risk assessment

Recently, The Lancet published a "Comment" with the title "Pyrethroid exposure: not so harmless after all" (Demeneix et al., 2020). We were surprised to see such a speculative article published by The Lancet. There is no critical evaluation of how the limited number of references (10) cited support – or failed to support - the authors' unjustified conclusions. The Editor of the Lancet and the manuscript reviewers seem to have made the naive assumption that the mere existence of a putatively hazardous substance in the human body invites restrictive regulation. The article may cause unwarranted public anxiety. Perhaps more importantly, this misguided position fails to satisfy the need for risk assessment which follows hazard identification and is the core of responsible regulatory policy.

The Lancet choose not to publish our criticism of their article. Thus, we are glad to have the opportunity to publish it in Toxicology Letters.

The 10 references of the commentary are excerpted as follows:

Reference 1. Bao et al. (2019) found the presence of 3-phenoxybenzoic acid (3-PBA) - the main metabolite of numerous pyrethroid insecticides – appears to be associated with a higher risk of mortality from all causes and specifically from cardiovascular disease in the US adult population. However, Bao et al. (2019) conclude they *"could not rule out the possibility of residual confounding by unmeasured or unrecognized factors"* and *"further studies are needed to replicate the findings and determine the underlying mechanisms"*.

Reference 2. Tang et al. (2018) describe how pyrethroids represent 30 % of the current global pesticide market and are widely used in agricultural and urban environments, in particular as biocides in homes and gardens. Accordingly, pyrethroid metabolites are frequently detected in the general population who are exposed through food, water, inhalation, or ingestion from residential use.

Reference 3. Soderlund (2012) summarizes the molecular mechanisms of neurotoxicity of pyrethroid insecticides. The insecticidal actions of pyrethroids depend on their ability to bind to and disrupt voltage-gated sodium channels as well as voltage-gated calcium and chloride channels of insect nerves. Since the structure, function, and pharmacology of voltage-gated sodium channels are highly conserved between insects and mammals, he concludes that it is not surprising that pyrethroids also alter the function of mammalian sodium channels, suggesting that actions on sodium channels are sufficient to account ***for the acute toxicity*** of this insecticide class. Whether chronic low pyrethroid exposure will also lead to neurotoxic effects in humans is not discussed.

Reference 4. Ye and Liu (2019) present a review of the effects of pyrethroids on the hypothalamic-pituitary-gonadal axis-related reproductive outcomes, which includes epidemiological investigations based on human biomonitoring, animal studies and *in vitro* tests. The authors conclude that *there is a significant gap between experimental animal data and human health effects. For example, the doses of pyrethroids used in animal experiments often far exceed realistic exposure levels in human, while the exposure durations of animals is usually much shorter than the realistic exposure durations of human. This may result in that animal experiment data are often inconsistent with the results observed in population studies. Therefore, it is necessary to increase the development of translational toxicology and to convert the findings of basic toxicological research into quantitative measurement of human health risk.*

Reference 5. Ye and Liu (2018) review many animal studies showing adverse effects of both urban-used (e.g., permethrin, cyfluthrin, bifenthrin) and agriculture-used (e.g., fenvalerate, cypermethrin, deltamethrin) pyrethroids. In animal studies, effects of pyrethroids on follicular cells, oocytes, uterus weight, length of estrous cycle were observed at dose levels between 4 mg/kg bwt and 200 mg/kg and hormone levels were affected at daily doses > 0.4 mg/kg. Increased FSH and LH levels have been reported between 3 μg/kg and 60 mg/kg, effects on the testes and testosterone levels between 0.2 and 150 mg/kg.

Evaluating the human data on the impact of pyrethroids on fertility and reproduction, the authors conclude that the findings between pyrethroids exposure and male reproductive parameters are inconsistent and cohort studies are needed to clarify the effects of pyrethroids exposure on male reproductive functions. Studies on pyrethroids exposure and pubertal development and HPG axis-secreted hormones in children are very limited as well.

Reference 6. Saillenfait et al. (2015) presents a comprehensive report on the use of pyrethroid insecticides, sources of human exposure and urinary concentrations of pyrethroid metabolites. For example, urinary 3-PBA concentrations of the general population in China, Europe, Japan North America, Antilles and Thailand range from 0.2 up to 2 μg/L, farmers up to 6.27 μg/L, textile workers up to 10 μg/L, forestry workers up to 4.41 μg/L and soldiers with permethrin impregnated uniforms up to 6.64 μg/L. Saillenfait concludes: *Numerous ambient monitoring data and analyses of pyrethroid metabolites in urine samples have shown widespread exposure to pyrethroids within the general population.*

http://dx.doi.org/10.1016/j.toxlet.2020.12.020

Insecticide residues in food and in indoor residential environments are major sources of exposure. Recently published human studies have raised concerns about the potential developmental and male reproductive toxicity of pyrethroids at environmental concentrations. Additional studies are necessary to further evaluate the long-term effects of pyrethroid exposure, especially in groups that may be regarded as being at special risk, such as children and pregnant women.

Reference 7. Hu et al. (2019) describe the key role of thyroid signaling in neurodevelopment and investigated maternal concentrations of circulating thyroid hormones in relation to pyrethroid exposure. An inverse dose-dependent relationship between urinary 3-phenoxybenzoicacid (3-PBA) and serum free T3 concentrations during the third trimester is reported. The median levels (interquartile range, IQR) for maternal serum TSH, TT3, FT3, TT4, FT4 were 1.83 (0.93–3.26) μIU/mL, 1.51 (1.18–1.81) ng/mL, 2.92 (1.97–3.48) pmol/L, 9.50 (8.16–10.83) μg/dL and 9.32 (6.06–11.79) pmol/L, respectively. However, it has to be noted that these hormone levels remain within the normal levels as published by the American Thyroid Association. Normal TSH levels in adults are 0.4–4 mU/L serum (slightly higher in pregnant women), in children between 1–20 weeks 0.58–5.57 mU/L, T4 in adults is 5.0–12.0 μg/dL, and T3 80–220 μg/dL.

Hu et al. critically conclude*: our study was limited by its cross-sectional design which was unable to establish a causal relationship between pyrethroid exposure and thyroid hormones. Besides, although we corrected several confounders that may disturb the relationships between pyrethroid exposure and serum thyroid hormones levels including demographic characteristics, lifestyle and seasonal variation, other potential confounding factors were still not taken into consideration such as household insecticide usage and other environmental pollutants.*

Reference 8. Chevrier et al. (2019) reviewed possible association between maternal peripartum concentrations of DDT/E and pyrethroid metabolites and thyroid hormone levels in neonates. In neonates, mean T4 was 5.2 μg/dL (standard deviation = 1.5) and the geometric mean of TSH was 1.2 μIU/mL (geometric standard deviation = 1.9). Individual values are not provided. The associations were substantially stronger among children from households below the South African food poverty line. However, studies conducted in Spain and Sweden found no association between maternal or cord DDT/E and neonatal TSH, free T4 or total T3, while inverse associations were reported between cord DDT/E and cord free or total T4 in Thailand. One study examining exposure to pyrethroids found no association between maternal urinary 3-PBA during pregnancy and TSH or free T4 among Japanese infants. Due to these controversial findings, the authors conclude that further research is needed to confirm these findings and examine whether they have implications for child development.

Reference 9. Hwang et al. (2019) reports the findings of a Korean National Environmental Health Survey to investigate the association between urinary 3-PBA levels and serum levels of T4 and T3 in a Korean adult population. Urinary 3-PBA levels were 3 times higher than those reported in Canada and the United States and levels showed a negative association with serum T4 in males and females. For T3, males demonstrated the same inverse association between urinary 3-PBA and T3, but females did not show such association. Among adults in the lower half of urinary 3-PBA levels, the association with T3 was significant, while that among the remainder was marginal. Again, the two thyroid hormone levels were within the normal range.

Reference 10. Wang et al. (2012) describe many pesticide formulations that contain piperonylbutoxide (PBO) to inhibit the metabolism of pesticides. Although EPA documents a low degree of concern for fetal susceptibility to the effects of PBO, the authors refer to a recent human epidemiologic study involving a population of pregnant women in the US, which found a significant association between PBO collected in their personal air during pregnancy and delayed mental development in the children. The children born to mothers who were more highly exposed to PBO during their pregnancy scored 3.9 points lower on the Mental Developmental Index compared with those with lower exposures. In neurodevelopment, Hedgehog signaling is crucial in regulating many processes in the development of the nervous system, including differentiation of the midbrain and ventral forebrain, and proliferation of hippocampal neuronal precursor cells. In this specific study, the authors demonstrate that in zebrafish embryos PBO binds to the seven-transmembrane receptor Smoothened (Smo) and inhibits Hedgehog signaling, which is a critical regulator of stem cell proliferation, cancer, and central nervous system development. Considering the widespread presence of PBO in the environment, the recent epidemiologic association of PBO exposure with delayed mental development in children, and the findings that PBO inhibits the Hedgehog signaling pathway, it is concluded that the safety profile of PBO needs to be investigated further.

Conclusions

It is surprising that a journal of The Lancet's standing would accept a review/comment based on the citation of few selected studies without a careful evaluation of their reliability in supporting the review's conclusions. None of the studies cited in the Lancet text comes to a firm conclusion based on validated experimental evidence. All recommend further studies to confirm or refute suggested associations, and none focuses on the importance of understanding the long-term effects of low exposure to pyrethroids in humans. The review/comment also failed to point out that the TSH and thyroid hormone levels in the studies considered usually remain within the normal range distribution in the population, nor did it mention a report by Roca et al. (2014) making clear that the urine of school children also contains a large number of metabolites from other pesticides besides those from pyrethroids.

We are dismayed by this uncritical attitude and feel compelled to point out that such unjustified reporting of what is a speculation on hazards undermines the rational analysis of human exposures and potential health risks in our complex environment.

Declaration of Competing Interest

The authors declare no conflict of interest.

References

Bao, W., Liu, B., Simonson, D.W., Lehmler, H.-J., 2019. Association between exposure to pyrethroid insecticides and risk of all-cause and cause-specific mortality in the general adult population. JAMA Interntl. Med. 180 doi:http://dx.doi.org/10.1001/jamainternmed.2019.6019 published online Dec 30.

Chevrier, J., Rauch, S., Obida, M., Crause, M., Bornman, R., Eskenazi, B., 2019. Sex and poverty modify associations between maternal peripartum concentrations of DDT/E and pyrethroid metabolites and thyroid hormone levels in neonates participating in the VHEMBE study, South Africa. Environ. Internatl. 131, 104958.

Demeneix, B., Leemans, M., Couderq, S., 2020. Pyrethroid exposure: not so harmless after all. Lancet Diabetes Endocrinol. doi:http://dx.doi.org/10.1016/S2213-8587(20)30039-5 Published Online February 13, 2020.

Hu, Y., Zhang, Z., Qin, K., et al., 2019. Environmental pyrethroid exposure and thyroid hormones of pregnant women in Shandong, China. Chemosphere 234, 815–821.

Hwang, M., Lee, Y., Choi, K., Park, C., 2019. Urinary 3-phenoxybenzoic acid levels and the association with thyroid hormones in adults: Korean National Environmental Health Survey 2012-2014. Sci. Total Environ. 696, 517–523.

Roca, M., Miralles-Marco, A., Ferré, J., Pérez, R., Yusà, V., 2014. Biomonitoring exposure assessment to contemporary pesticides in a school children population of Spain. Environ. Res. 131, 77–85.

Saillenfait, A.M., Ndiaye, D., Sabate', J.P., 2015. Pyrethroids: exposure and health effects-an update. Int. J. Hyg. Environ. Health 218, 281–292.
Soderlund, D.M., 2012. Molecular mechanisms of pyrethroid insecticide neurotoxicity: recent advances. Arch. Toxicol. 86, 165–181.
Tang, W., Wang, D., Wang, J., Wu, Z., Li, L., Huang, M., Xu, S., Yan, D., 2018. Pyrethroid pesticide residues in the global environment: an overview. Chemosphere 191, 990–1007.
Wang, J., Lu, J., Mook Jr., R.A., Zhang, M., Zhao, S., Barak, L.S., Freedman, J.H., Lyerly, H. K., Chen, W., 2012. The insecticide synergistic piperonyl butoxide inhibits hedgehog signaling: assessing chemical risks. Toxicol. Sci. 128, 517–523.
Ye, X., Liu, J., 2018. Effects of pyrethroid insecticides on hypothalamic-pituitary-gonadal axis: a reproductive health perspective. Environ. Pollut. 245, 590–599.

Frank A. Barile[a]
Sir Colin Berry[b]
Bas Blaauboer[c]
Alan Boobis[d]
Herrmann Bolt[e]
Christopher J. Borgert[f]
Wolfgang Dekant[g]
Daniel Dietrich[h]
Jose L. Domingo[i]
Gio Batta Gori[j]
Helmut Greim[r,*]
Jan Hengstler[e]
Sam Kacew[k]
Hans Marquardt[l]
Olavi Pelkonen[m]
Kai Savolainen[n]
Pat Heslop-Harrison[o]
Aristides Tsatsakis[p]
Nico P. Vermeulen[q]

[a] *College of Pharmacy and Health Sciences, St John's University, Queens, New York, USA*

[b] *Queen Mary University of London, UK*

[c] *Division of Toxicology, Institute for Risk Assessment Sciences, Utrecht University, Utrecht, The Netherlands*

[d] *National Heart & Lung Institute, Imperial College, London, UK*

[e] *Leibniz Research Centre for Working Environment and Human Factors (IfADo), TU Dortmund, Dortmund, Germany*

[f] *Applied Pharmacology and Toxicology, Inc. Gainesville, FL, USA*

[g] *Department of Toxicology, University of Wuerzburg, Wuerzburg, Germany*

[h] *Faculty of Biology, University of Konstanz, Konstanz, Germany*

[i] *Laboratory of Toxicology and Environmental Health, School of Medicine, IISPV, Universitat 'Rovira i Virgili', Reus, Spain*

[j] *The Health Policy Center, Bethesda, Maryland, USA*

[k] *McLaughlin Centre for Risk Assessment, University of Ottawa, Ottawa, Canada*

[l] *Toxicology, Hamburg, Germany*

[m] *Department of Pharmacology and Toxicology, University of Oulu, Oulu, Finland*

[n] *Nanosafety Research Centre, Finnish Institute of Occupational Health, Helsinki, Finland*

[o] *Department of Genetics and Genome Biology University of Leicester, Leicester, UK*

[p] *Department of Toxicology, Medical School, University of Crete, Greece*

[q] *Department of Chemistry & Pharmaceutical Sciences, Vrije Universiteit, Amsterdam, The Netherlands*

[r] *Technical University of Munich, Munich, Germany*

* Corresponding author.
E-mail address: helmut.greim@mytum.de (H. Greim).

Received 16 December 2020

Available online 4 January 2021