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LETTER TO EDITOR

Piperonylbutoxide and the Necessity of Toxicological Assessment of Insecticide Mixtures; a Letter to Editor

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Dear Editor;

With great interest we read the letter by Dr. Faress et al. (1) in which they explain the clinical impression of pyrethroid poisoning in relation to the addition of piperonylbutoxide (PBO). The authors include our case report of an insecticide spray formulation containing cypermethrin, tetramethrin and PBO that induced a myocardial infarction type II in a patient with cardiac comorbidity (2). We fully agree with the authors that the "presence or absence of piperonylbutoxide" may induce different types of pyrethroid poisoning and determination of all suspicious ingredients is "necessary for all clinical toxicologists". However, we think it is necessary to discuss the current assessment of PBO, and to analyze in detail some of the case reports cited.

The toxicology of PBO and other derivatives of methylenedioxybenzene has been evaluated since the late 1960s, with the general finding that the longer the side chain of the parent substance, the less toxic the compound (3). PBO with its two long side chains is assumed to be tolerated in higher single doses, and the acute oral LD50 for rats is higher than 2 g/kg body weight (3, 4)for the derivative piperonal higher than 2 g/kg, compared to 0.5 g/kg for the parent methylenedioxybenzene (3). In human volunteers an oral single PBO dose of at mean 0.71 mg/kg body weight did not cause signs of toxicity (5). The substance PBO underwent several detailed toxicity assessments e.g. by the European Chemicals Agency (ECHA), world health organization (WHO), Food and Agriculture Organization (FAO), and US Environmental Protection Agency (US EPA) (4, 6). Various scenarios of acute and chronic expositions, including oral, inhalative, and dermal exposure have been evaluated to define acceptable exposure levels or concentrations. The inhalative absorption of PBO has been considered to be 100%, and the dermal absorption up to 4.8% (4). The systemic short-term acceptable exposure level (AEL) of PBO is 1.0 mg/kg body weight/day (6) (11-fold higher compared to the systemic AEL value of 0.088 mg/kg/d of cypermethrin).

Given these relatively high tolerated doses, it is worthwhile to look closer at the literature quoted by Dr. Faress et al. The cited case report by Babic et al. (7) is the only publication of a possible cardiotoxic effect of PBO alone. A thorough analysis revealed that the mentioned 63-year-old patient sprayed a" PBO based" formulation indoors within 30 minutes, while wearing improvised mouth-nose-protection. After admittance to hospital with sinus bradycardia, piperonal as decomposition product of PBO was detected in his serum. Unfortunately, neither the serum level nor the product ingredients and their concentrations were provided in this case report. If the formulation did not contain another active ingredient (usually an insecticide, e.g. pyrethroid), the PBO was probably used in a high dose and led to an extraordinary high exposure via inhalation and dermal route. Two other case reports cited by Dr. Faress et al. refer to pyrethroids and subsequent bradycardia: One patient developed a transient sinus arrest following a suicide attempt by a mixture of prallethrin 1.6% (a synthetic pyrethroid) and PBO 5% (8), and the other patient exhibited a third-degree atrioventricular block after exposure to a pyrethroid-containing insecticide (9). Another interesting reference of Dr. Faress et al. is a five-year review on pyrethrin and pyrethroid illnesses in the northwest of the USA (10). It summarizes 407 patients and illustrates the potential severity of poisoning with a fatal case following accidental indoor inhalation of esfenvalerate (3.5%) and pyrethrins (1.0%) formulated with piperonyl butoxide.

A review of human PBO incident reports by the US EPA in 2004 indicates a greater risk for moderate and major symptoms (e.g. respiratory symptoms like bronchospasm, cough/choke, and dyspnoea) by products containing pyrethrins and PBO than by pyrethrins alone (4, 11). Two reports on pesticide-related illness and injury due to non-occupational (12) and occupational (13) pesticide use

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in the United States 2007-2011 showed that pyrethroids and pyrethrins were the substances most frequently responsible for the toxic effects, regarding both single and multiple substances. An analysis of related clinical effects associated with the pyrethroids cypermethrin and tetramethrin revealed cardiovascular effects in 2% of the cases and respiratory effects in 22% of 12.039 cases (cypermethrin) and 17% of 21.414 cases (tetramethrin) (14).

We think there are four issues against an acute cardiotoxicity solely attributable to PBO: 1) There is evidence for toxic effects by pyrethroids alone and combined with PBO; 2) The mode of action of PBO is completely different from that of pyrethroids, as PBO inhibits the cytochrome p450 system and delays the detoxification of insecticides, whereas pyrethroids alter voltage-gated sodium channels, which occur in both neuronal and cardiac cells (15). This may explain some of the cardiotoxic effects (16), but a cascade of DNA fragmentation, apoptosis and inflammation has been investigated recently in rats (17). 3) In contrast, a mechanism that explains acute cardiac side effects of PBO has not yet been published. This is in line with the figure 1 by Dr. Faress et al. that explains possible adrenergic effects by delayed clearing of pyrethroids. 4) The AOEL (acceptable operator exposure level) for acute inhalation of PBO is about 32-fold higher than the AOEL of cypermethrin. Concerning the active substances discussed in our case report, PBO had a comparably low concentration of 0.51%, and the concentrations of the pyrethroids were 0.68% cypermethrin, and 0.1% tetramethrin.

In summary, we would like to supplement the findings of Dr. Farress et al. by noting that there is evidence that PBO enhances the toxic effects of pyrethroids. However, one must also acknowledge that a cardiotoxic effect of PBO alone remains unproven. We strongly support the statement of the authors that knowledge all suspicious agents of insecticides is indispensable. Furthermore, we reiterate our recommendation for a more rigorous evaluation of active substance mixtures (18) and the need for international harmonization.

1. Declarations

1.1. Acknowledgments

None declared.

1.2. Authors' contributions

Both BH and DH reviewed the literature, wrote and revised the manuscript. Both authors read and approved the final version of manuscript.

1.3. Availability of data

The data that support the findings of this study are available on request from the corresponding author.

1.4. Using artificial intelligence chatbots

None.

1.5. Funding

None.

1.6. Conflicts of interest

The authors declare no conflict of interest.

1.7. Using artificial intelligence chatbots

This letter was written without application of AI chatbots.

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