Response to 'Piperonyl Butoxide: Friend or Foe'

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Dear Editor,

In response to the February 2025 editorial by Vardavas et al.[1], 'Piperonyl Butoxide: Friend or Hidden Foe', we would like to offer clarification on several points where the discussion of piperonyl butoxide (PBO) does not fully reflect the current scientific and regulatory understanding. We focus on three principal areas.

Contextualization of toxicological findings

The editorial attributes various effects to PBO such as hepatocellular necrosis, altered exploratory behavior, developmental endpoints, and male fertility effects – without providing essential dose-response context or relevance to human exposures. These findings arise largely from non-guideline animal studies at doses far higher than human exposures. Without evaluating dose, mode of action, species differences, and human exposure estimates, the text overstates potential human health concerns.

Updated carcinogenicity assessment

The editorial cites a mode of action (MOA) publication that refers to a 79-week mouse bioassay reporting increased hepatocellular adenomas[2]. Missing, however, is the conclusion that the MOA demonstrates that these tumors lack human relevance. The European Chemicals Agency's (ECHA) Committee for Risk Assessment (RAC) 'considers the established MOA plausible, although some data gaps remain and limitations were seen in the mechanistic studies. Nevertheless, the concern for human relevance is lowered by the data provided, which is further substantiated by the relatively low number of carcinomas observed in one sex only. Therefore, no classification for carcinogenicity is warranted'[3].

Similarly, the editorial mentions PBO's now outdated classification by the U.S. Environmental Protection Agency (EPA) as a 'possible human carcinogen based on limited evidence of carcinogenicity in animals'; however, the EPA reclassified PBO in July 2024 as 'Not likely to be carcinogenic to humans at doses that do not induce cellular proliferation in the liver'[4].

Human exposure data and respiratory effects

The editorial references the 2006 EPA PBO Registration Eligibility Decision regarding potential respiratory effects of pyrethrin/PBO products but does not include later human surveillance data that directly address these concerns[5].

First, analyses of American Association of Poison Control Centers (AAPCC) Toxic Exposure Surveillance System (TESS) data from 2001–2003 evaluated dermal and respiratory symptoms following exposures to pyrethrins formulated with PBO[6]. The authors concluded that these products are associated with a relatively low risk of adverse effects and are unlikely to trigger reactions in individuals with asthma or allergies.

Second, the Pyrethrins Stewardship Program (PSP), conducted from 2010–2016, systematically assessed symptomatic dermal and inhalation exposures to pyrethrins used with other pyrethroids and synergists, including PBO[7]. This comprehensive surveillance program concluded that: 1) adverse respiratory or dermal events following product exposure were rare; 2) most dermal or respiratory effects were minor and self-limiting; and 3) pyrethrin-containing products, including those formulated with synthetic pyrethroids and/or synergists like PBO, do not pose a significant risk of serious dermal or respiratory reactions, even among individuals with reported allergies or asthma.

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Conclusion

A balanced evaluation of PBO requires consideration of mechanistic research, updated regulatory determinations, and real-world human exposure data. When these lines of evidence are integrated, they provide a scientifically grounded characterization of PBO's favorable safety profile.

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CONFLICTS OF INTEREST

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ETHICAL APPROVAL AND INFORMED CONSENT

Ethical approval and informed consent were not required for this study.

DATA AVAILABILITY

Data sharing is not applicable to this article as no new data were created.

PROVENANCE AND PEER REVIEW

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