Journal of Medical Entomology, XX(XX), 2025, 1–6
https://doi.org/10.1093/jme/tjaf042
Research

ENTOMOLOGICAL SOCIETY OF AMERICA
SHARING INSECT SCIENCE GLOBALLY

OXFORD

Behavior, Chemical Ecology

Effects of aging and cleaning on bed bug (Hemiptera: Cimicidae)-derived histamine

Simona Principato*, and Zachary C. DeVries

Department of Entomology, University of Kentucky, Lexington, KY, USA

*Corresponding author. Department of Entomology, University of Kentucky, 1100 S. Limestone St., S-225 Agricultural Science Center North, Lexington, KY 40546, USA (Email: s.principato@uky.edu).

Subject Editor: Warren Booth

Received on 21 January 2025; revised on 25 February 2025; accepted on 3 March 2025

Bed bugs (*Cimex lectularius* L.) are common indoor pests found in close association with humans. Bed bug feces have been identified as the primary source of indoor environmental histamine, an emerging contaminant that could pose a potential threat to human health. Therefore, it is critical that we understand the stability of histamine in homes, along with mitigation strategies so that we can reduce exposure and potential health risks. In this study we characterized histamine stability over time on 2 surfaces (unfinished wood, fabric), discovering that aging histamine at room temperature, over the course of 9 mo, showed no significant changes in the level of this biogenic amine. As histamine appears slow to degrade on its own, we evaluated the efficacy of various cleaning methods for reducing or removing histamine from these surfaces. The most effective histamine cleaning methods on fabric were bleach, hydrogen peroxide, and a laundry cycle, while multi-purpose cleaner, bleach, and hydrogen peroxide were the most effective on unfinished wood. Overall, histamine reduction was most influenced by more aggressive cleaning methods (hard scrubbing) or cleaners known for removing stains (hydrogen peroxide, bleach). The results of this study will enhance our ability to reduce exposure to this emerging contaminant.

Keywords: allergen, contaminant, histamine mitigation, cleaning method, bed bug

Introduction

Exposure to indoor allergens can cause significant human health problems (Salo et al. 2008, Lynch et al. 2014). Allergic diseases and the exacerbation of disease morbidity in allergen-sensitized individuals have been primarily associated with indoor allergens originating from arthropods, such as cockroaches, house dust mites, and environmental contaminants like mold (Grant et al. 2023). Bed bugs (*Cimex lectularius* L.) are also known to cause health problems, specifically dermatitis in humans (Usinger 1966). This insect has made a resurgence over the past 25 yr, with infestations reported worldwide in homes, hotels, and public transportation (Romero et al. 2007). Although bed bugs are not known to transmit diseases, the Environmental Protection Agency (EPA) defines them as pests of significant Public Health importance (Lai et al. 2013). The health implications involving bed bug infestations are not limited to the onset of skin bites, but psychological distress is also often reported (Goddard and deShazo 2012, Susser et al. 2012).

More recently, bed bugs were found capable of excreting histamine (biogenic amine) in their feces as a component of their aggregation pheromone (Gries et al. 2015). The histamine excretion potential of bed bugs was assessed, revealing that adult female bed bugs excrete more than 8 µg of histamine per day, with histamine levels being associated with blood intake (Gaire et al. 2022). Bed bug-derived histamine can accumulate in the environment and be detected in the dust even 3 mo after bed bugs are eradicated (DeVries et al. 2018). It was also observed that environmental histamine has a clear spatial distribution in homes, being found in high levels primarily in dust from bedrooms/sleeping areas where bed bugs are typically found in the highest concentrations (Gordon et al. 2023). Additionally, indoor histamine was found in air vents, which may increase the risk of human exposure to it by inhalation (Gordon et al. 2023). Although other hematophagous hemipterans, such as kissing bugs, tropical bed bugs, and bat bugs, also excrete histamine, indoor histamine in the United States can be primarily linked to bed bugs. (Principato et al. 2023).

Histamine is known to be a mediator of the immune response in the human body and can contribute to the onset or exacerbation of allergic diseases like asthma (Branco et al. 2018). The potential effects of human exposure to environmental histamine, either by contact or inhalation, have not yet been assessed. However, some research found that keratinocytes and lung epithelial cells exposed to histamine in vitro led to the production of molecules involved in an immunological response, suggesting that allergic reactions may occur in vivo (Takizawa et al. 1995, Gschwandtner et al. 2013). Therefore, it is possible that exposure to bed bug-derived histamine could induce respiratory or dermatological allergies or could increase sensitivity in allergic individuals by exacerbating their allergic reaction.

Due to the potential health risk associated with exogenous histamine, there is a need to understand how to mitigate histamine levels indoors. Therefore, we evaluated both the stability of histamine indoors along with different histamine removal methods, focusing on common substrates of upholstery and furniture that would be found in homes. Furthermore, we evaluated the impacts of various pest control strategies on histamine stability. The results of this study are discussed in relation to current best bed bug management practices, with an emphasis on incorporating strategies to reduce human exposure.

Materials and Methods

Bed Bug Rearing

A laboratory, insecticide-susceptible population of bed bugs (Harold Harlan, collected from Ft. Dix, NJ in 1973) was used for all the bioassays. Bed bugs were reared in 177 ml plastic containers (Consolidated plastics, Stow, Ohio, USA) under standard laboratory conditions (23 to 25°C, 30 to 50% RH, and a photoperiod of 12:12 (L:D) h). Bed bugs were fed weekly on human blood (Kentucky Blood Center, Lexington, KY, USA) containing the anticoagulant citrate phosphate dextrose (CPD), using an artificial feeding system (Gaire et al. 2022).

Substrate Conditioning by Bed Bugs

Three materials commonly found in homes, and that bed bugs are likely to condition with feces, were used for the bioassays: cotton jersey fabric (Joann Fabric and Crafts, Lexington, KY, USA), unfinished basswood (Basswood, FSWCCK, Wuxi, Jiangsu, China), and cotton sheets (California Design Den, Fremont, CA, USA). To condition substrates, 5 adult male bed bugs were fed as described above and then immediately placed onto a 3.8 cm^2 area of substrate for 7 d. Bed bugs were maintained in this area using a 12-well cell culture plate (Biologix, Camarillo, CA, USA), with each well representing a single replicate whose assignment to each treatment or control was made randomly. After 7 d, bed bugs were removed and conditioned materials were stored in the freezer (−20°C) until testing (generally within a week but up to 3 mo).

Histamine Stability Over Time

Unfinished basswood and cotton jersey fabric were evaluated for histamine stability. Substrates were conditioned as previously described, and after removal of the bed bugs, substrates were stored in open top containers on the benchtop and aged for 0, 3, 6, and 9 mo under laboratory conditions (23 to 25°C, 30 to 50% RH). Six replicates were done for each time point and substrate type.

Cleaners and Treatments

Multiple cleaners/treatments were tested to evaluate their efficacy in removing/reducing histamine from cotton jersey fabric and unfinished wood. Treatments were selected to represent compounds or procedures that histamine might be exposed to indoors. Where appropriate, the label directions were used for dilution and application. Treatments included (with final applied active ingredient concentration): water (with and without rubbing), bleach (1.5% sodium hypochlorite; The Clorox Company, Oakland, CA, USA), enzyme cleaner (≤ 0.39% C9-11,Ethoxylated; Multi-Purpose Enzyme Cleaner, Amazon, Seattle, WA, USA), white vinegar (ALDI, Essen, Germany), steam (Cimex Eradicator, Polti USA Inc. Los Angeles, CA, USA), vacuum removal (Eureka, Midea America Corp, Parsippany, NJ, USA), multi-purpose cleaner concentrate (0.06% Citrus terpenes; EcoSafe Labs, Dallas, TX, USA), steri-fab (0.11% 1-Decanaminium, N-decyl-N,N-dimethyl-, chloride, 0.08% Alkyl* dimethyl benzyl ammonium chloride, 60.39% Isopropyl alcohol, 0.22% Phenothrin; Noble Pine Products CO, Yonkers, NY, USA), hydrogen peroxide (3%; PL Developments, Clinton, SC, USA), pesticide application (0.06% lambda-cyhalothrin; Demand, Syngenta, Basel, Switzerland), heat (Oven, Fisher Scientific, Pittsburgh, PA, USA), and laundry cycle (ESTATE washer, Whirlpool, Benton Harbor, MI, USA). Both positive controls (substrates that were conditioned but did not receive treatment) and negative controls (substrates that were neither conditioned nor treated) were included.

Cleaning Methods—Soft Cleaning

A gentle cleaning method (soft cleaning) was initially employed to assess the effectiveness of each treatment. Treatments were performed by immersing a paper towel (Tork Multifold paper towel, Essity, Stockholm, Sweden) into the substance used for cleaning. After squeezing the excess liquid, the paper towel was forcibly rubbed on the bed bug-conditioned substrate 3 times. This procedure was used for water, vinegar, bleach, the enzyme cleaner, steri-fab, hydrogen peroxide, and the multi-purpose cleaner. Water was also tested by just spraying it onto the conditioned surface (~1 ml per 117 cm^2), without rubbing it.

The steamer was set at the maximum temperature of 180°C and while being held at ~3 cm distance from the substrate to be treated, it was passed 3 times at a speed of 3 cm/s. The vacuum was applied with direct contact to the surface (brush nozzle), and it was passed 3 times at a speed of 3 cm/s. Substrates were let dry for 24 h after treatment, then either stored in the freezer (−20°C) or analyzed for histamine. Five replicates were done for each treatment and control.

Cleaning Methods—Deep Cleaning

The soft cleaning treatments that resulted in a significant reduction in histamine levels were then re-evaluated using a more intensive cleaning method (deep cleaning). This was done to evaluate the importance of physical removal in the reduction of histamine. Water (rubbing) was also evaluated (regardless of significance). Deep cleaning was performed by forcibly rubbing the surface for 60 s (30 rubs, or 10× more rubbing than the soft cleaning method) using a paper towel immersed in the cleaning agent. It should be noted that this method resulted in a visible reduction in fecal spots (SP personal observation, not quantified). Conditioned unfinished basswood was treated with water, enzyme cleaner, vinegar, multi-purpose cleaner, bleach, and hydrogen peroxide. Conditioned cotton jersey fabric was treated with water, multi-purpose cleaner, bleach, and hydrogen peroxide.

In addition, a laundry cycle treatment with or without the use of a standard household laundry detergent (Tide pods, Procter & Gamble, Cincinnati, OH, USA) was used for cotton jersey fabric and cotton sheets. Conditioned samples were placed in the washing

machine together with the rest of the unconditioned sheets and washed for 40 min on a hot cycle.

Pest Control Methods

Heat was delivered by placing the conditioned substrates in the oven (Fisher Scientific, Pittsburgh, PA, USA) for 4 h at 130°F, as verified by a temperature data logger (HOBO UX100-003, Onset Computer Corporation, Bourne, MA, USA). The pesticide (Demand) was diluted per label instructions and applied at a volume of ~1 ml per 117 cm^2 without rubbing the surface.

Histamine Analysis

Histamine was quantified using gas-chromatography mass-spectrometry (GC-MS) as described by Principato et al. (2023). Briefly, the substrates were collected and placed individually in 20 ml plastic vials (Fisher Scientific, Hampton, NH, USA) to which 5 ml of HPCL-grade water (VWR International LLC, Radnor, PA, USA) was added. 10 µg of mass-labeled histamine (histamine-α,α,β,β-d4; CDN Isotopes, Quebec, Canada) was then added as an internal standard (in 0.1 M HCL; Macron Fine Chemicals, Radnor, PA, USA) and the samples were put on a nutating rocker (Labnet International, Iselin, NJ, USA) for 10 min. A volume of 1 ml aliquot from each sample was collected for histamine extraction and placed into a 4-ml glass vial (VWR Chemicals, Radnor, PA, USA) to which 1 ml of toluene (VWR Chemicals, Radnor, PA, USA) and 2 ml of buffer solution (pH 12; Honeywell International Inc, Charlotte, NC, USA) were added. Histamine was derivatized by adding 100 µl of isobutyl-chloroformate (Alfa Aesar, Haverhill, MA, USA) to the samples, placing them on the nutating rocker for 45 min, and then centrifuging them for 10 s at 400 g. The supernatant was then transferred into a 2-ml glass vial (Fisher Scientific, Hampton, NH, USA) and evaporated under N_2 until dryness and then resuspended in 1 ml of toluene (VWR Chemicals, Radnor, PA, USA). Samples were then stored at –20°C until analysis.

Histamine was quantified from samples using an Agilent Technologies 8860 GC (Santa Clara, CA), connected to a 5977B MS, and operated in pulsed splitless mode (15 psi for 0.5 min, then 6 psi) with an inlet temperature of 280°C. The instrument was equipped with a 30 m × 0.25 mm × 0.25 µm HP-5MS UI column (Agilent Technologies) and helium was used as the carrier gas at a flow rate of 1.5 ml/min. A temperature of 100°C was set for the oven and the temperature increased at a rate of 30°C/min until it reached 320°C, then held at this temperature for 5 min. The following parameters were set for the GC-MS: transfer line temperature was 280°C, MS quadrupole temperature was 150°C, and the MS source temperature was 230°C. The parameters for the internal standard (m/z 197) and histamine (m/z 194) retention time were 6.32 min. A 13-point calibration curve ranging from 0.1 to 100 µg/ml was used for the internal standard quantification method. The method of detection limit was determined as previously described by Principato et al. (2023) and was 0.16 µg/1 ml of toluene.

Statistical Analysis

Histamine stability over time and pest control interventions were analyzed using analysis of variance (ANOVA) followed by Tukey's test. ANOVA was also used to analyze the effect of cleaning on histamine levels, followed by Dunnet's test to compare the histamine level following each cleaning method to the untreated control. Student *T*-tests were performed to compare histamine levels between soft and deep cleaning for those treatments where both cleaning methods were used. Kruskal–Wallis test, followed by the Dunn test, was used to analyze histamine levels for the laundry treatment. All analyses were done using R Studio and significance was determined as $P < 0.05$.

Results

Histamine Stability Over Time

Aging did not significantly affect the amount of histamine present in cotton jersey fabric ($F = 1.67$, df = 3, 20, $P = 0.20$; Fig. 1A). However, aging did have a significant effect on histamine levels in unfinished basswood ($F = 5.59$, df = 3, 20, $P = 0.006$; Fig. 1B), although only histamine levels at 6 mo were found to be significantly lower than baseline, with all other times not significantly different from each other (including samples aged for 9 mo). Overall, the histamine levels declined slightly over time on both cotton jersey fabric and unfinished basswood with levels decreasing from 74.5 µg at baseline to 67.7 µg on cotton jersey and from 87.3 µg at baseline to 60.7 µg on basswood at 9 mo (Fig. 1). The only statistically significant decline was at 6 mo on basswood with an average measured level of ~44 µg on 6 replicates. These data indicate that histamine levels on these surfaces are stable over time.

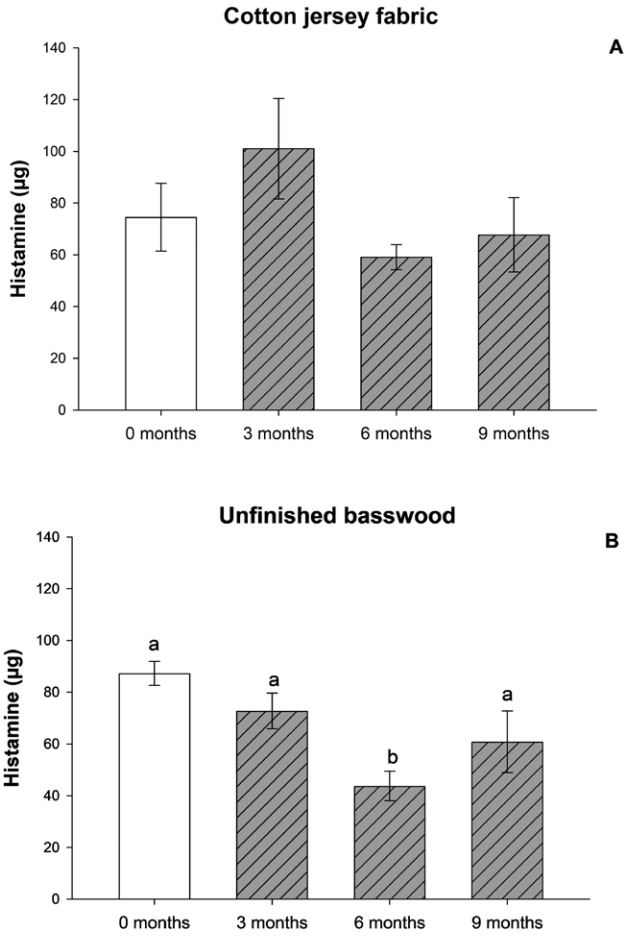

Fig. 1. Effect of histamine aging on (A) cotton jersey fabric and (B) unfinished basswood. Error bars represent the standard error of the mean (SEM). Different lower-case letters indicate significant differences among aging times ($P < 0.05$, ANOVA followed by Tukey's test). No significant differences were detected for cotton jersey fabric (ANOVA, $P > 0.05$).

Efficacy of Cleaning Methods in Reducing/Removing Histamine from Substrates

Soft cleaning treatment (cleaning method or product application) had a significant effect on histamine levels when applied to both cotton jersey fabric ($F = 8.4$, df = 10, 44, $P < 0.001$; Fig. 2A) and unfinished basswood ($F = 11.18$, df = 10, 44, $P < 0.001$; Fig. 2B). For soft cleaning on cotton jersey fabric, only the multi-purpose cleaner, bleach and hydrogen peroxide resulted in a significant reduction in histamine levels compared to the untreated positive control (Fig. 2A). For soft cleaning on unfinished basswood, the following treatments resulted in a significant reduction in histamine levels compared to the untreated positive control: water (rubbing), enzyme cleaner, vinegar, multi-purpose cleaner, bleach, and hydrogen peroxide (Fig. 2B).

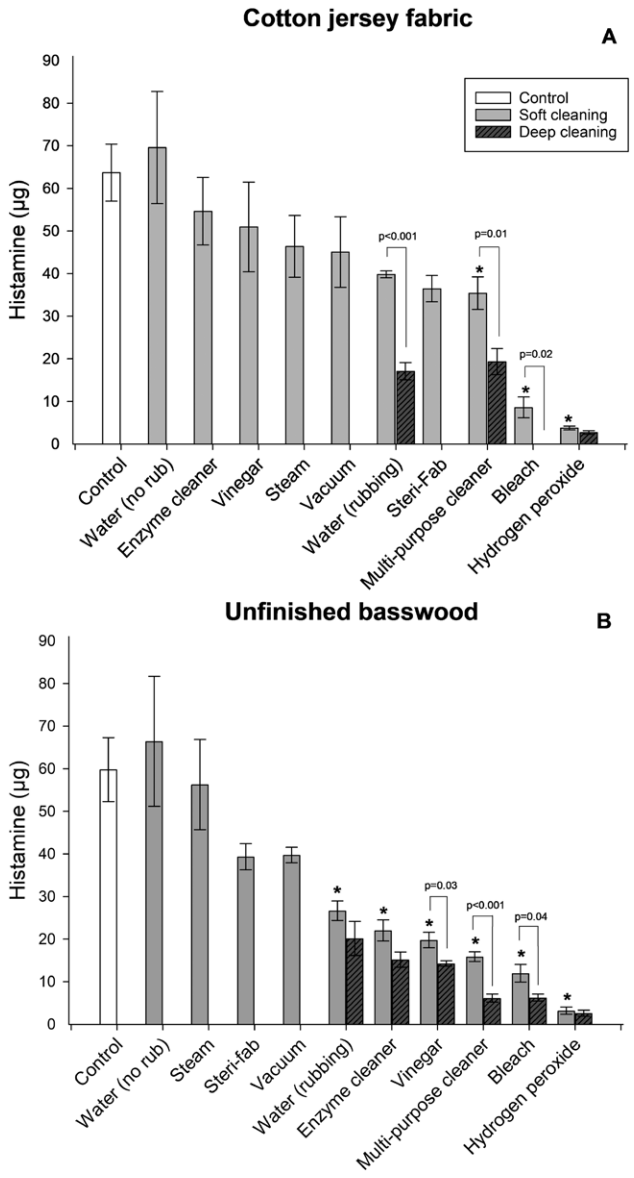

Fig. 2. Efficacy of soft and deep cleaning methods in reducing histamine from (A) cotton jersey fabric, and (B) unfinished basswood. Error bars represent the standard error of the mean (SEM). Significant differences ($P < 0.05$) of soft cleaning methods from the controls (ANOVA followed by Dunnett's test) are indicated with an "*." Significant differences between soft and deep cleaning (Student's *T*-test) are shown with brackets and the accompanying *P*-value.

Deep cleaning treatment (cleaning method or product application) had a significant effect on histamine levels when applied to both cotton jersey fabric ($F = 28.49$, df = 3,16, $P < 0.001$; Fig. 2A) and unfinished basswood ($F = 12.63$, df = 5, 24, $P < 0.001$; Fig. 2B).

When comparing soft and deep cleaning methods applied to cotton jersey fabric, a significant reduction of histamine was achieved for the multi-purpose cleaner ($t = 3.2$, df = 7.6, $P = 0.01$) and bleach ($t = 3.5$, df = 4, $P = 0.02$), but not for hydrogen peroxide ($t = 1.7$, df = 7.9, $P = 0.12$) (Fig. 2A). Interestingly, a significant reduction was also observed through deep cleaning with water only on cotton jersey fabric in comparison to soft cleaning with water ($t = 10.4$, df = 5.2, $P < 0.001$; Fig. 2A).

When comparing soft and deep cleaning methods applied to unfinished basswood, deep cleaning only resulted in significant declines in histamine for vinegar ($t = 2.86$, df = 4.98, $P = 0.03$; Fig. 2B), multi-purpose cleaner ($t = 6.54$, df = 7.7, $P < 0.001$; Fig. 2B), and bleach ($t = 2.54$, df = 5.2, $P = 0.04$; Fig. 2B).

In addition to soft and deep cleaning, another treatment that successfully removed histamine was laundering cotton sheets ($X^2 = 12.1$, df = 2, $P = 0.002$; Table 1) and cotton jersey fabric ($X^2 = 13.3$, df = 2, $P < 0.0001$; Table 1). Laundering both with and without the use of detergent resulted in significantly less histamine.

Effect of Pest Control Interventions on Histamine Stability

Pest control interventions (heat, pesticide [Demand]) did not significantly reduce the amount of histamine compared to the untreated positive controls for either cotton jersey fabric ($F = 0.14$, df = 2, 12, $P = 0.86$; Fig. 3A) or unfinished basswood ($F = 1.39$, df = 2, 12, $P = 0.28$; Fig. 3B).

Discussion

Results of this study showed that histamine can persist for up to 9 mo, at room temperature. This aligns with the findings of previous studies which found that histamine can be detected in house dust even 3 mo after the eradication of an infestation (DeVries et al. 2018). Despite some fluctuations in histamine levels over time, degradation seems to be a slow process. Thus, histamine appears to be stable and does not break down on its own.

Using only soft cleaning, some cleaning methods were found to be effective at reducing or removing histamine from both cotton jersey fabric and unfinished basswood. On cotton jersey fabric, significant reductions in histamine were achieved with the multi-purpose cleaner, bleach, and hydrogen peroxide. On unfinished basswood, most treatments were effective, including water (rubbing), enzyme cleaner, vinegar, multi-purpose cleaner, bleach, and hydrogen peroxide. However, upon further testing, we found deep cleaning

Table 1. Efficacy of laundry cycle at reducing histamine

	Cotton Jersey Fabric	Sheets
Treatment	Histamine (µg) ± SEM[1,2]	Histamine (µg) ± SEM[1,2]
Control	55.8 ± 6.7[a]	106.6 ± 8.9[a]
With detergent	0 ± 0.0[b]	1.3 ± 0.3[b]
Without detergent	0 ± 0.0[b]	0 ± 0.0[b]

[1]SEM represents the standard error of the mean.

[2]Values followed by different letters indicate significant differences based on the Kruskal–Wallis test ($P < 0.05$).

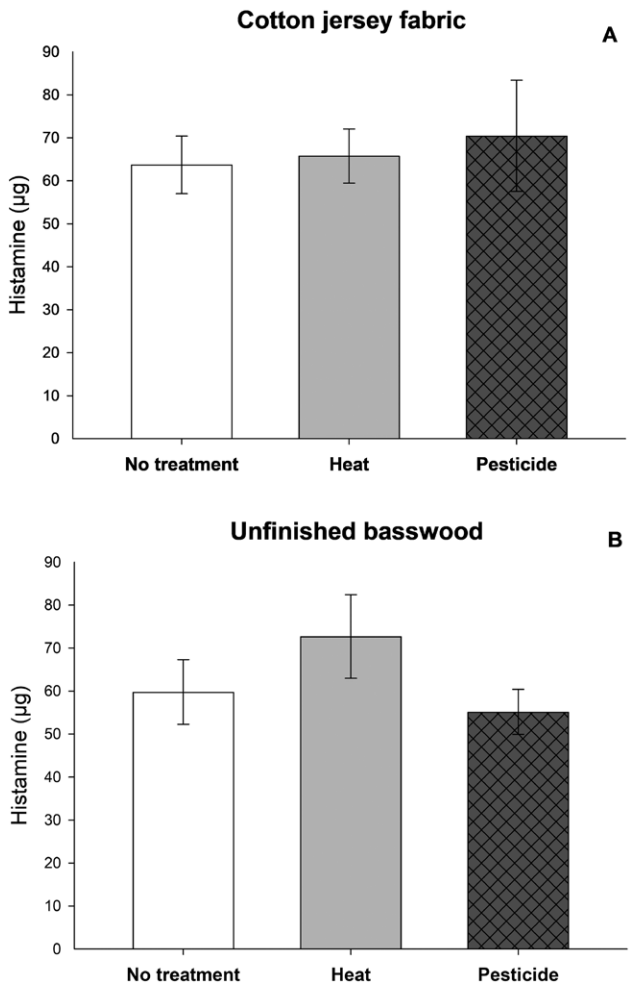

Fig. 3. Effect of pest control interventions with heat and a pesticide (Demand) on the level of histamine on (A) cotton jersey fabric and (B) unfinished basswood. Error bars represent the standard error of the mean (SEM). No significant differences were detected (ANOVA, $P > 0.05$).

to cause significant reductions compared to soft cleaning for most treatments tested (cotton jersey fabric: water [rubbing], multipurpose cleaner, and bleach; unfinished basswood: vinegar, multipurpose cleaner, and bleach). These results suggest that the reduction of histamine on substrates is primarily driven by the removal of bed bug feces, as evidenced by the varying effectiveness between soft and deep cleaning methods, although it should be noted that hydrogen peroxide nearly eliminated histamine on both surfaces even when applied as a soft cleaning method.

Histamine is present in bed bug feces as a less volatile component of the aggregation pheromone (Gries et al. 2015) whose quantity released in the feces can vary depending on the life stages of the bed bug, mating status, and time after feeding (Gaire et al. 2022). Its quantity in the environment can be significant as bed bugs are the primary source of histamine indoors (Principato et al. 2023) and on average one male bed bug can excrete about 5 µg of histamine per day (Gaire et al. 2022). Removing feces (either chemically or physically) appears to be essential for reducing histamine levels. In contrast, methods that do not actively eliminate the feces, such as using steam, vacuuming, and water without rubbing do not result in significant changes in histamine levels. It should also be noted that while the removal of feces is important, not all feces are visible, and in situations where histamine is detected on surfaces without visible fecal spots, there are likely clear fecal spots, which are generally numerous and not easily seen with the naked eye (Wilson and Miller 2022).

Despite the observed reductions, it should be noted that for all treatments, surfaces, and cleaning methods (soft, deep), only bleach and hydrogen peroxide resulted in histamine levels below our limit of detection. This could be due to the nature of bed bug feces. Bed bug feces are primarily composed of digested blood/blood components (Berenger and Parola 2016). In our study, we found great efficacy for bleach and hydrogen peroxide, which are common products used to remove blood stains. This efficacy is probably due to their ability to break down the proteins in blood, which could have facilitated the removal of histamine.

There was also considerable variation in the efficacy of the cleaning methods tested, possibly due to the type of substrate, characteristics of histamine, and the type of cleaning method used. Substrates like fabric may more deeply absorb bed bug feces, making fecal removal more difficult, possibly explaining why some treatments were more effective on unfinished wood compared to fabric. Histamine is readily soluble in acidic solutions but does not easily dissolve in alkaline solutions. However, our data suggest that both alkaline (eg bleach) and acidic (eg hydrogen peroxide) cleaners can reduce histamine, therefore, pH is not a great predictor for the efficacy of a product in mitigating histamine from surfaces.

In addition to surface cleaning, we also explored laundering. Almost complete removal of histamine was achieved with the laundering of cotton jersey fabric or cotton sheets, regardless of the use of detergent. The agitation and mechanical action of the washing machine may have helped to scrub the fabric, leading to a physical lift and loosening the fecal particles regardless of the use of detergent. Given these results, more aggressive cleaning techniques should be explored to determine if complete removal can be achieved outside of laundry or deep cleaning with bleach or hydrogen peroxide.

Common pest control interventions, like the use of heat treatments or pesticides, did not show any effect in lowering the amount of histamine from either type of substrate. This is not surprising since histamine is known to be heat stable (Durak-Dados A and J 2020), and degradation occurs at above 200°C (Kodchakorn et al. 2021). Standard pest control heat treatments would not reach this high temperature; thus, histamine is unlikely to degrade. The ineffectiveness of pesticides in lowering the amount of histamine is probably due to the lack of physical action and the lack of chemical properties to break down proteins in the blood, as they are not designed for stain removals.

Numerous studies have shown that histamine in food remains stable and unaffected by common cooking methods, such as salting, smoking, drying, vacuum packaging, and thawing (Shulpekova et al. 2021) and it also withstands pasteurization and cooking, leading to histamine intolerance in some individuals (Ferrante and Mercogliano 2023). However, to our knowledge, the stability and mitigation of histamine in the environment, where exposure occurs primarily through contact or inhalation, have not been explored, despite histamine being commonly found in the dust of occupational environments like dairy barns, where its presence was suggested to cause respiratory issues (Kullman et al. 1998).

In addition to concerns about possible health effects, applying the appropriate cleaning method to remove or reduce histamine from the environment could help diminish potential aggregation sites as histamine is a component of the aggregation pheromone in bed bugs and serves as an arrestant (Gries et al. 2015). Newly introduced bed bugs may struggle to establish a population in a new environment if they do not settle near a host. By eliminating feces and histamine from previous infestations, we may decrease the likelihood of bed

bugs finding suitable hiding spots that could support their settlement. That said, these ideas require further investigation.

In conclusion, the results of this project highlight that successful reduction of histamine is achieved by aggressive cleaning methods (hard scrubbing) and cleaners known for removing stains (hydrogen peroxide, bleach). While histamine accumulated in house dust and air vents may be easier to manage through vacuuming the dust and replacing air vent filters, the challenge lies in cleaning surfaces where feces become embedded in the substrate. It is important to note that reducing histamine relies also on completely eliminating the bed bug infestation as cleaning will not prevent the depositing of new fecal material in the environment. The most effective way to limit exposure to environmental histamine is to remove it both during the infestation (even though new fecal spots will appear) and after the infestation has been eradicated.

These findings emphasize the importance of incorporating deep cleaning strategies in bed bug management practices to ensure histamine removal, especially in bedding areas where people spend considerable time and histamine levels are significantly higher than in other parts of the home. Although clinical data on a "safe" exposure level for bed bug-derived histamine is currently unavailable, reducing histamine from homes will help minimize human exposure to this potentially harmful environmental contaminant while also eliminating a key component of the bed bug aggregation pheromone from the environment.

Acknowledgments

We would like to thank the members of the DeVries lab for their help in rearing the bed bugs for the experiments.

Author contributions

Simona Principato (Conceptualization [equal], Data curation [lead], Formal analysis [lead], Investigation [lead], Visualization [lead], Writing—original draft [lead], Writing—review & editing [equal]), and Zachary C. DeVries (Conceptualization [equal], Formal analysis [supporting], Funding acquisition [lead], Project administration [equal], Resources [lead], Visualization [supporting], Writing—original draft [supporting], Writing—review & editing [equal])

Funding

This work was funded in part by the National Institutes of Health through the NIH Director's Early Independence Award (DP5-OD028155 to ZCD). This work was also supported in part by the Bill Gatton Foundation (ZCD), the Kerri Casner Environmental Sciences Fellowship (SP), and scholarships from the Pest Management Foundation and Pi Chi Omega (SP). The content is solely the responsibility of the authors and does not necessarily represent the official views of the sponsors.

Conflicts of interest. None declared.

References

Berenger J-M, Parola P. 2016. Arthropod vectors of medical importance. Infect Dis (Auckl). 4th ed. Elsevier. p. 104–112. https://doi.org/10.1016/B978-0-7020-6285-8.00012-5.

Branco A, Yoshikawa FSY, Pietrobon AJ, et al. 2018. Role of histamine in modulating the immune response and inflammation. Mediat. Inflamm. 2018:9524075. https://doi.org/10.1155/2018/9524075.

DeVries Z, Santangelo RG, Barbarin AM, et al. 2018. Histamine as an emergent indoor contaminant: accumulation and persistence in bed bug infested homes. PLoS One. 13:e0192462. https://doi.org/10.1371/journal.pone.0192462.

Durak-Dados A, Michalski M, Jacek O. 2020. Histamine and other biogenic amines in food. J. Vet. Res. 64:281–288. https://doi.org/10.2478/jvetres-2020-0029.

Ferrante MC, Mercogliano R. 2023. Focus on histamine production during cheese manufacture and processing: a review. Food Chem. 419:136046. https://doi.org/10.1016/j.foodchem.2023.136046.

Gaire S, Principato S, Schal C, et al. 2022. Histamine excretion by the common bed bug (Hemiptera: Cimicidae). J. Med. Entomol. 59:1898–1904. https://doi.org/10.1093/jme/tjac131.

Goddard J, deShazo R. 2012. Psychological effects of bed bug attacks (*Cimex lectularius L.*). Am. J. Med. 125:101–103. https://doi.org/10.1016/j.amjmed.2011.08.010.

Gordon JM, Santangelo RG, González-Morales MA, et al. 2023. Spatial distribution of histamine in bed bug-infested homes. Sci. Total Environ. 880:163180. https://doi.org/10.1016/j.scitotenv.2023.163180.

Grant TL, Wood RA, Chapman MD. 2023. Indoor environmental exposures and their relationship to allergic diseases. J. Allergy Clin. Immunol. Pract. 11:2963–2970. https://doi.org/10.1016/j.jaip.2023.08.034.

Gries R, Britton R, Holmes M, et al. 2015. Bed bug aggregation pheromone finally identified. Angew. Chem. 127:1151–1154. https://doi.org/10.1002/ange.201409890.

Gschwandtner M, Mildner M, Mlitz V, et al. 2013. Histamine suppresses epidermal keratinocyte differentiation and impairs skin barrier function in a human skin model. Allergy 68:37–47. https://doi.org/10.1111/all.12051.

Kodchakorn K, Nimmanpipug P, Phongtamrug S, et al. 2021. Experimental confirmation of proton conductivity predicted from intermolecular hydrogen-bonding in spatially-confined novel histamine derivatives. J. Solid State Chem. 299:122182. https://doi.org/10.1016/j.jssc.2021.122182.

Kullman G, Thorne P, Waldron P, et al. 1998. Organic dust exposures from work in dairy barns. Am. Ind. Hyg. Assoc. J. 59:403–413. https://doi.org/10.1080/15428119891010668.

Lai O, Ho D, Glick S, et al. 2013. Bed bugs and possible transmission of human pathogens: a systematic review. Arch. Dermatol. Res. 308:531–538. https://doi.org/10.1007/s00403-016-1661-8.

Lynch SV, Wood RA, Boushey H, et al. 2014. Effects of early-life exposure to allergens and bacteria on recurrent wheeze and atopy in urban children. J. Allergy Clin. Immunol. 134:593–601.e12. https://doi.org/10.1016/j.jaci.2014.04.018.

Principato S, Romero A, Lee C-Y, et al. 2023. Histamine excretion in common indoor and hematophagous arthropods. J. Med. Entomol. 60:1269–1277. https://doi.org/10.1093/jme/tjad103.

Romero A, Potter MF, Potter DA, et al. 2007. Insecticide resistance in the bed bug: a factor in the pest's sudden resurgence? J. Med. Entomol. 44:175–178. https://doi.org/10.1603/0022-2585(2007)44[175:IRITBB]2.0.CO;2.

Salo PM, Arbes SJr, Crockett PW, et al. 2008. Exposure to multiple indoor allergens in US homes and its relationship to asthma. J. Allergy Clin. Immunol. 121:678–684. e672. https://doi.org/10.1016/j.jaci.2007.12.1164.

Shulpekova YO, Nechaev VM, Popova IR, et al. 2021. Food intolerance: the role of histamine. Nutrients 13:3207. https://doi.org/10.3390/nu13093207.

Susser SR, Perron S, Fournier M, et al. 2012. Mental health effects from urban bed bug infestation (*Cimex lectularius L.*): a cross-sectional study. BMJ Open. 2:e000838. https://doi.org/10.1136/bmjopen-2012-000838.

Takizawa H, Ohtoshi T, Kikutani T, et al. 1995. Histamine activates bronchial epithelial cells to release inflammatory cytokines in vitro. Int. Arch. Allergy Immunol. 108:260–267. https://doi.org/10.1159/000237162.

Usinger RL. 1966. Monograph of Cimicidae (Hemiptera, Heteroptera). Entomological Society of America.

Wilson MM, Miller DM. 2022. Quantification of fecal spot production as a measure of environmental contamination based on common bed bug (Hemiptera: Cimicidae: *Cimex lectularius* L.) population size. J. Econ. Entomol. 115:1637–1649. https://doi.org/10.1093/jee/toac069.