Science of the Total Environment 880 (2023) 163180

Contents lists available at ScienceDirect

Science of the Total Environment

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

Short communication

Spatial distribution of histamine in bed bug-infested homes

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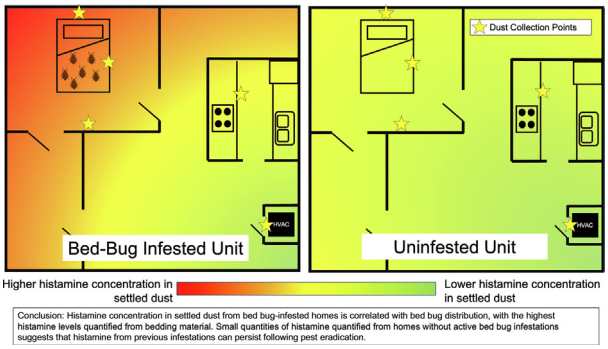
HIGHLIGHTS

- Significantly greater histamine quantified from bed bug-infested homes
- Highest histamine quantified from bed and bedroom
- Some histamine quantified from uninfested homes, likely from previous infestations

GRAPHICAL ABSTRACT



ARTICLE INFO

Editor: Philip K. Hopke

Keywords:
Environmental contaminants
Insects
Asthma
Cimex lectularius
Respiratory health

ABSTRACT

Histamine is a component of the bed bug aggregation pheromone. It was recently identified as an environmental contaminant in homes with active bed bug infestations, posing a potential health risk to humans via skin contact or inhalation. It remains unclear how histamine is distributed in homes and if histamine can become airborne. In the present study, histamine levels in household dust were quantified from multiple locations within bed bug infested and uninfested apartments. Bed bug population levels were quantified using both traps and visual counts. The amount of histamine detected varied significantly with respect to sampling location, with the highest concentration of histamine quantified from bedding material. Infestation severity did not have a significant effect on histamine quantified at any location. Our results indicate that the bedroom should be the primary focus of histamine mitigation efforts, although histamine can be found throughout the home. Histamine quantified from homes without active bed bug infestations suggests that histamine from previous infestations can persist following pest eradication. These findings highlight the importance of histamine as a potential insect allergen and will be important for the development of targeted mitigation strategies of bed bug histamine.

1. Introduction

Indoor inhalant allergens pose significant risk to human health due to a disproportionate amount of time spent indoors by a majority of the U.S. population. In a 2001 study by the U.S. Environmental Protection Agency (EPA), it was estimated that Americans spend nearly 87 % of their time inside buildings (Klepeis et al., 2001). Therefore, mitigation of indoor allergens such as house dust mite (HDM) (Gøtzsche and Johansen, 2008; Celedón et al., 2007; Sporik et al., 1990; Sears et al., 1989; Fernández-Caldas, 2002), dander from dogs and cats (Sears et al., 1989; Ingram et al., 1995; Wood et al., 1989; Perzanowski et al., 2002), cockroaches (Eggleston et al., 1998; Chew et al., 2008; Arbes et al., 2003; Arbes et al., 2004; Arruda, 2005; Arruda et al., 2001; Chapman et al., 1996), pollen

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http://dx.doi.org/10.1016/j.scitotenv.2023.163180
Received 23 February 2023; Received in revised form 26 March 2023; Accepted 26 March 2023
Available online 29 March 2023

(Most recent national asthma data, 2018; D'Amato et al., 2020; Li et al., 2020; Schenk et al., 2006) and mold/fungus (Sears et al., 1989; Dales et al., 2000; Pulimood et al., 2007; Suphioglu, 1998) is critical to the management of asthma and its symptoms. Of the arthropod-generated allergens, those from HDM and cockroaches have been well studied (Gøtzsche and Johansen, 2008; Celedón et al., 2007; Sporik et al., 1990; Sears et al., 1989; Arbes et al., 2004; Arruda, 2005; Arruda et al., 2001; Chapman et al., 1996; Prevalence of Asthma, 2018; Gore and Schal, 2007; Pomés et al., 2017a; Pomés and Schal, 2020; Pomés et al., 2007; Sever et al., 2007; Tovey et al., 1981; Pomés et al., 2017b) with considerable research on their production (Arruda, 2005; Pomés and Schal, 2020; Chad Gore and Schal, 2004), introduction into the environment (Eggleston et al., 1999a; Custovic et al., 1994), and mitigation (Arbes et al., 2003; Arbes et al., 2004; Sever et al., 2007; Eggleston, 2005; Eggleston et al., 1999b). The impacts of HDM and cockroaches on the development and exacerbation of asthma are clear, as is the need to assess emerging biocontaminants produced by indoor arthropod pests and their negative health impacts.

One clear arthropod-associated pathway that merits further investigation is the recently-discovered association between environmental histamine, an identified modulator of allergy and immune response, and the common bed bug, *Cimex lectularius* (Gries et al., 2015; DeVries et al., 2018). Histamine has been identified as a component of the bed bug aggregation pheromone (Gries et al., 2015), a chemical blend, deposited in bed bug feces, that attracts bed bugs. As part of the pheromone, histamine acts as a non-volatile arrestant (Gries et al., 2015). Subsequently, histamine was identified in indoor dust, specifically dust from the floor behind the bed, within bed bug-infested homes, with substantially lower concentrations of histamine from uninfested homes (DeVries et al., 2018); these results demonstrated that bed bugs were the source of exogenous histamine within the infested homes. In fact, all life stages of bed bugs were recently found capable of excreting histamine, with excretion being highest 3–4 days following a blood meal (Gaire et al., 2022). Overall, these findings suggest that as bed bug populations grow, the amount of histamine introduced into household dust will increase rapidly.

Histamine plays a critical role in several physiological processes within mammalian systems (Panula, 2021). Most notably, histamine and its receptors impact the immune system, mediating allergic and inflammatory response (Branco et al., 2018; Lieberman, 2011). Activation of select G protein-coupled histamine receptors is believed to mediate inflammation in an immune response, with histamine receptors such as Histamine Receptor 1 (H_1) correlated with bronchoconstriction characteristic of asthma illness (Yamauchi and Ogasawara, 2019). Synthesized from histidine and released by mast cells upon activation, histamine is strongly associated with allergic asthma, where asthma symptoms, including increased production and accumulation of mucus, and inflammation within the airways (Krystel-Whittemore et al., 2016), can develop from exposure to an inhalant allergen. This can lead to increased bronchial hypersensitivity and even airway hypertrophy over time (Chetty and Nielsen, 2021; Keglowich and Borger, 2015), which can have serious impacts on respiratory health. Negative health impacts following ingestion of consumables such as fish, meat, dairy, and alcoholic beverages due to elevated histamine in these products have been identified (Bodmer et al., 1999) and histamine in agricultural dust has been cited by several studies as a potential health risk (Siegel et al., 1992; Siegel et al., 1991; Kullman et al., 1998).

The identification of histamine production by all bed bug life stages (Gries et al., 2015; Gaire et al., 2022), a strong association between histamine levels in household dust and bed bug infestation (DeVries et al., 2018), and the persistence of histamine in homes (DeVries et al., 2018) suggest that bed bugs have the potential to impact respiratory health. The present study investigates the distribution of histamine within homes infested with bed bugs and examines whether the severity of infestation impacts the concentration of histamine within infested homes.

2. Materials and methods

2.1. Study design and sampling

Bed bug-infested ($n = 17$) and uninfested ($n = 23$) apartments were identified and recruited from multi-family housing complexes in Raleigh, NC. Infestation status was determined through 30 min visual inspections conducted by two study team members that primarily focused on sleeping surface where bed bugs usually harbor, but also included other areas of the home: the floor directly behind the bed, the remaining bedroom floor, kitchen floor, and the in-home heating, ventilation, and air conditioning (HVAC) air filter. In addition, four traps (Climbup Interceptor, Susan McKnight Inc., Memphis, TN), were deployed as described in DeVries et al. 2018 (DeVries et al., 2018). "Infested" homes were those with either visual confirmation of live bed bugs and/or bed bug trap catch across the duration of the study. Homes were considered "uninfested" if no live or dead bed bugs were seen or trapped during the study period, and residents did not indicate having a previous infestation. Dust samples were collected from the bed, the floor behind the bed, the remaining bedroom floor, kitchen floor, and the HVAC air filter. The "bedroom" was defined as the room where the resident primarily slept and the "bed" was defined as the specific furnishing where the individual slept (e.g., could have been a couch or armchair). Settled dust samples (wall behind the bed, bedroom floor, and kitchen floor) were collected for 2 min using a Eureka Mighty-Mite 9.0-ampere vacuum cleaner fitted with a Dustream collector and filter (40 μm, Indoor Biotechnologies Inc., Charlottesville, VA). The kitchen sample was collected by vacuuming the perimeter of the room and the bedroom floor sample comprised of the perimeter of the bed, but not the wall behind the bed, which was sampled separately. Air filter dust samples and bed dust samples were collected using the sample protocol and equipment from existing HVAC air filters and the bedding material (seams of the mattress and the fitted sheet), respectively. All dust samples were placed into glass vials and stored at −80 °C.

Infested apartments ranged from two to >100 bed bugs collected over the 1-week trapping period used in this study. For each infested apartment, the infestation severity was ranked as follows: "High Infestation" = bedbugs observed AND > 10 bed bugs trapped, "Medium Infestation" = bed bugs observed AND < 10 bed bugs trapped, "Low Infestation" = bed bugs observed but NO bed bugs trapped within our study, there were no homes in which bed bugs were trapped but not visually observed. Of the 17 infested units, four were considered "Low", six were considered "Medium", and seven were considered "High".

2.2. Histamine analysis

Dust samples were processed and analyzed for histamine following the protocol outlined in DeVries et al. (2018). Briefly, the total mass of each dust sample was taken following sifting through 450 μm mesh to remove large particulates. Sieves and sifting tools were cleaned thoroughly with detergent and 70 % ethanol between each sample to prevent contamination. Samples that contained <10 mg of sieved dust were not included in further analysis. After sieving, a 10–50 mg sample of sieved dust was added to a 4 mL plastic centrifuge tube (Sarstedt Inc., Nümbrecht, Germany), along with 1 mL of HPLC grade water and an internal standard of 10 μg of histamine-α,α,β,β-d4 2HCl (Sigma-Aldrich Co. LLC, St. Louis, MO) in 0.1 M HCl. Next, the sample was mixed on a nutating mixer for 10 min, followed by centrifugation at 437*g*. The supernatant was transferred to a 4 mL glass vial and combined with 1 mL of toluene (VWR, Avantor, Radnor, PA, USA), 2 mL of alkaline buffer (di-sodium hydrogen phosphate/sodium hydroxide solution; pH 12.0 at 20 °C; Honeywell Fluka, NJ), and 100 μL of isobutyl chloroformate (IBCF; Sigma-Aldrich Co. LLC, St. Louis, MO). Isobutyl chloroformate functioned as a derivatization agent which allowed our samples to be analyzed via Gas Chromatography-Mass Spectrometry (GC–MS). Samples were mixed on a nutating mixer for 45 min, before being centrifuged for 30 s to separate the aqueous and organic layers. The organic top layer was moved to a clean 2 mL glass vial (Fisher Scientific

Inc.) and blown to dryness on a hot plate (30 °C) under low-flow high-purity nitrogen gas. Samples were then re-suspended in toluene (Suprasolv, Merck, Darmstadt, Germany) and stored at −15 °C until analysis.

All extracted and derivatized samples were analyzed using a GC (8860 GC System, Agilent Technologies, Santa Clara, CA) coupled with a MS (5977B MSD, Agilent Technologies). Samples (1 μL) were injected into an ultra inert quartz liner packed with silanized glass wool (Agilent Technologies) which led to a J&W HP-5 ms Ultra Inert Column (30 m × 0.25 mm × 0.25 μm; Agilent Technologies). The system was run in pulsed splitless mode using He as the carrier gas, with an initial injection pressure of 40 psi (splitless) for 2 min, followed by a purge flow of 40 mL/min to the split vent, with a volumetric flow rate of 1.5 mL/min after 2 min. The oven temperature program increased from 100 °C to 300 °C at 30 °C/min, with a final hold of 5 min. Quantification ions were *m/z* 194 for histamine and *m/z* 197 for histamine-α,α,β,β-d4, and samples were fitted to a 10-point calibration curve (ranging from 0.1 μg/mL to 100 μg/mL) to quantify histamine. The limit of detection was determined as ~3.2 ng/mg dust. All samples quantified below this limit were assigned a value of 0.

2.3. Statistical analysis

All statistical analyses were conducted in R version 3.6.2 (R Development Core Team, 2021). Data were cube-root transformed for analysis to meet the assumptions of normality, as needed. Using data from infested homes alone, the effect of sampling locations was analyzed using Analysis of Variance (ANOVA). The relationship between histamine concentrations and distance from the bed was further explored by ranking sampling location by distance from the bed bug epicenter, with "0" assigned to bedding material, "1" assigned to the wall behind the bed, "2" assigned to the bedroom floor, "3" assigned to the kitchen, and "4" assigned to the air filter. Linear regression was used to determine the relationship between location rank and cube root-transformed histamine concentration. Tukey's post hoc test was used for pairwise comparisons. Visualization of sampling location differences was generated through the ggplot2 package in R (Wickham, 2016). Finally, differences based on infestation status (infested vs. uninfested) were determined using one-sided *t*-tests. Differences by infestation severity were examined for each sampling location using Kruskal-Wallis tests.

3. Results

Within infested homes, location had a significant effect on the abundance of histamine ($F = 9.3589$, df = 4,65, $p < 0.001$), with the greatest quantities collected from the bed, compared to the wall, floor, kitchen, and air filter (Fig. 1). Histamine concentrations in vacuum samples collected from the bed differed from histamine in vacuum samples collected from all other sampling locations, while histamine concentrations did not differ between samples collected from the wall behind the bed and samples collected from the remaining perimeter of the bedroom floor. Finally, there were no differences in histamine quantified from bedroom floor samples, kitchen samples, and dust samples collected from the air filter (Fig. 1). We found a significant, negative relationship between histamine concentration and distance from the bed, with histamine concentration declining with increased distance from the bed (histamine concentration = 4.8967 + −1.0901*location rank, $R^2 = 0.34$, $F_{1, 68} = 37.24$, $p < 0.0001$).

To compare histamine between infested and uninfested homes, mean μg histamine/g sieved dust was calculated for each home using all sampling locations. Infested homes ($n = 17$) significantly differed from uninfested homes ($n = 23$) ($t = 3.844$, df = 38, $p = 0.0002$). Infestation status had a significant impact on histamine abundance for bed/bedding material ($t = 3.151$, df = 21, $p = 0.0024$) and for the floor behind the bed ($t = 2.323$, df = 33, $p = 0.0132$), and the remaining bedroom floor ($t = 2.022$, df = 35, $p = 0.0254$). Infestation status did not significantly impact histamine quantified from dust collected from the kitchen ($t = 0.0201$, df = 27, $p = 0.4210$) or the air filter ($t = -1.137$, df = 31, $p = 0.8680$) (Table 1).

Infestation severity within infested homes did not significantly impact quantified histamine at any of the sampling locations (bed: $\chi^2 = 0.836$, df = 2, $p = 0.658$; wall behind the bed: $\chi^2 = 0.458$, df = 2, $p = 0.795$; bedroom floor: $\chi^2 = 1.562$, df = 2, $p = 0.458$; kitchen: $\chi^2 = 4.573$, df = 2, $p = 0.102$; air filter: $\chi^2 = 2.740$, df = 2, $p = 0.254$.

4. Discussion

Histamine was found to increase in concentration with proximity to the bed, with the highest concentration observed in the bed/bedding material. Given that the bed is the typical location where residents spend most of their time and thus where the highest concentration of bed bugs typically occurs (Doggett et al., 2018), this is not surprising. Furthermore, bed bug histamine excretion is driven by blood consumption, so not only are bed bugs more concentrated in and around the sleeping areas, they are also more likely to take, digest and defecate a blood meal in these locations resulting in greater histamine excretion (Gaire et al., 2022). The detection of histamine in the kitchen suggests either the presence of some bed bugs in the kitchen, or translocation of histamine from the bedroom to other rooms. Bed bugs have been found to move throughout the home, including into the kitchen (Cooper et al., 2015), which supports the possibility bed bugs in the kitchen are producing histamine. However, the translocation of histamine from areas of the home via clothes, shoes, or the movement of items between rooms could be responsible for histamine in kitchen dust samples, which should be explored further.

The presence of histamine in the air filters, albeit at lower concentrations than in other sampling locations, suggests that histamine can become airborne, possibly in association with small dust particles. However, the lack of significance between histamine recovered from air filters in uninfested and infested homes suggests that, though it becomes incorporated into household dust, histamine being spread throughout the home as airborne particles is not as significant a mode of histamine translocation as we had initially thought. Further research is needed to determine mechanisms of histamine movement throughout the home, as well as the potential for spread of histamine between adjacent apartments. Inhalant histamine is uncommon, but it has been identified as a potential hazard in organic agricultural dust in several studies and hypothesized to be sourced through bacteria, animal excrement and contaminants within hay (Siegel et al., 1992; Siegel et al., 1991; Kullman et al., 1998). Further studies are needed to determine the mechanisms that allow histamine to become airborne. The peritrophic membrane coating the fecal pellet has been hypothesized to be a barrier to the release of allergens associated with HDM, and, to a lesser degree, those associated with cockroaches, into airborne dust (Esposito et al., 2011). Insects in the order Hemiptera, to which the common bed bug belongs, lack a defined peritrophic membrane (Silva et al., 2004; Terra and Ferreira, 1994; Ashbrook et al., 2022), which may allow histamine within the feces of bed bugs to become airborne more easily. It is also important to note that the frequency of air filter replacements in the units surveyed in this study is unknown. The same is true for other locations we surveyed; for example, we do not know when bed sheets were last changed and the floors cleaned. Therefore, future quantification of the dynamics of histamine generation and its concentration in air will require the use of active sampling methods.

When comparing each sampling location, between infested and uninfested homes, we similarly found that histamine concentration in household dust differs significantly by location for bedding, behind the bed, and bedroom floor samples, with nearly a 20-fold difference between infested and uninfested homes in the case of the samples collected from bedding material (Table 1). However, the differences in the lower histamine concentrations from kitchen and air filter samples between infested and uninfested homes were non-significant. In our study, bed bug-infested homes had an average histamine concentration of 16 μg histamine/100 mg dust from samples collected behind the bed, which is much less compared to previous findings from the same sampling location in

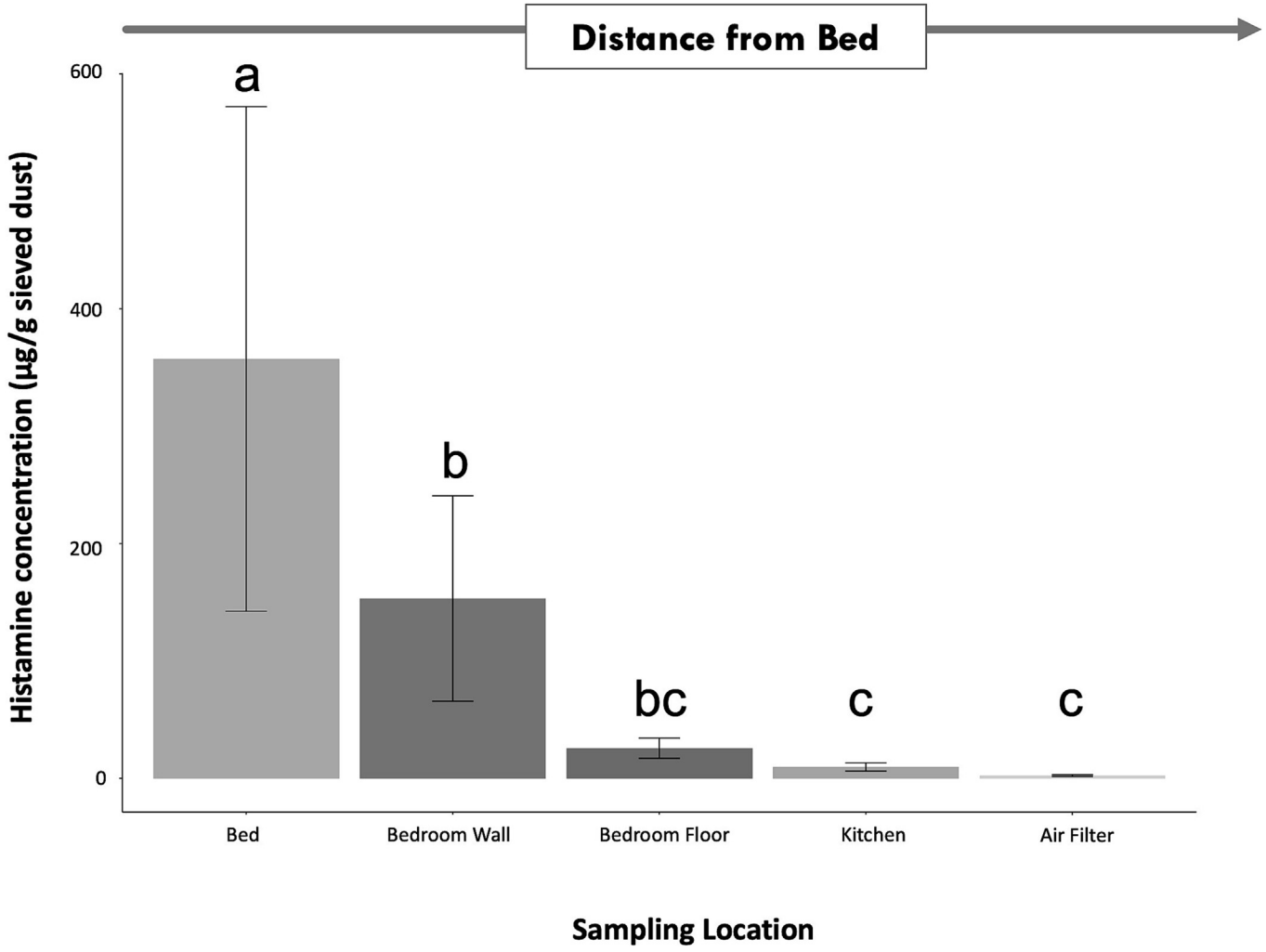

Fig. 1. Differences in histamine concentration in dust samples collected at different locations within bed bug-infested homes ($n = 17$). Bars represent mean histamine concentrations and brackets indicate standard error of the mean. Different letters correspond to significant differences between locations based on post-hoc comparisons (Tukey's test) on cube-root transformed data. Locations are ordered left to right with increasing distance from the bed.

different homes (54 µg/100 mg dust; (DeVries et al., 2018)). This discrepancy may be due to a number of factors highlighted throughout this discussion (e.g., resident cleaning, historical bed bug infestations). Histamine quantified in this study from all but the air filter and kitchen in uninfested homes was, on average, higher than histamine concentrations in hay dust that have been identified as a concern for respiratory health (0.5 ng/mg hay dust; (Siegel et al., 1991)). Histamine found within our study is also significantly higher than produced from human skin and skin with atopic dermatitis (196 ± 30 ng/mg protein and 262 ± 68 ng/mg protein, respectively; (Ruzicka and Glück, 1983)). This supports previous hypotheses that, while bed bugs are likely not the only source of histamine within the indoor environment, because of the large populations of bed bugs in severe infestations and the comparatively high levels of histamine an individual bed bug can produce (Gaire et al., 2022), bed bugs are likely the primary source of histamine within the home. This is also supported by recent studies that have shown most common indoor arthropods do not excrete histamine at all (DeVries, unpublished data).

Table 1
Mean µg histamine/g sieved dust for sampling locations within infested and uninfested homes. * denotes significant differences between infested and uninfested units at that location based on one-sided *t*-tests.

Location	Infested mean µg histamine/g dust; ±SE	Uninfested mean µg histamine/g dust; ±SE	Ratio: infested/uninfested
Bed*	357.20 ± 214.77	17.92 ± 9.77	19.9×
Bedroom wall*	153.27 ± 87.48	37.08 ± 23.35	4.1×
Bedroom floor*	25.78 ± 8.58	5.97 ± 1.07	4.3×
Kitchen	9.75 ± 3.5	6.10 ± 1.27	1.6×
Air filter	2.46 ± 0.75	5.03 ± 1.30	0.5×

Although our results show that histamine can be detected from in-unit air filters, suggesting that histamine becomes airborne to some extent, it does not appear histamine dispersal is significantly mediated by heating, ventilation, and air conditioning (HVAC) systems. Portable oscillating fans are frequently used within homes, which may increase dust movement from source deposits and thus facilitate histamine movement into the air column. Vacuuming has been shown to stir up settled dust and increase exposure to dustborne allergens (Kalra et al., 1990) and further studies have demonstrated no differences between vacuums with or without high-efficiency particulate-arrest (HEPA) filters on dust mite allergen exposure (Gore et al., 2006). Use of vacuums in bed bug-infested homes may have similar impacts on bed bug histamine exposure and increase histamine loads within indoor air, although this has not been tested.

Within infested homes, we surprisingly did not find a relationship between infestation severity and histamine quantified from collected dust in any of the locations we sampled. While our study was limited by our sample sizes for each infestation severity ranking, the lack of a detailed history of bed bugs within the homes sampled also makes it difficult to interpret

relationships between current infestation severity rank and histamine abundance. Without the ability to fully assess historical population dynamics of bed bugs, homes which represented "low" infestations within the context of our scoring metrics may have experienced higher population sizes that decreased with treatment prior to inclusion in our study, which could not be accounted for. Furthermore, histamine's relative stability in household dust (DeVries et al., 2018) makes long-term knowledge of infestation history essential to associating infestation size with histamine levels. As demonstrated in this study, it may be even insufficient to have bed bug history from a single resident, as bed bug infestations, and therefore histamine within a home, could pre-date current residents. Homes without active bed bug infestations might have had previous active infestations that were eradicated, suggesting that longevity of bed bug histamine within the home will need to be explored further. Discrepancies seen in our study in terms of infestation status and histamine quantified may have also been due to inadvertent histamine mitigation from cleaning conducted by the resident. As we continue to develop targeted mitigation strategies for bed bug histamine, it will be crucial to evaluate the efficacy of cleaning methods (vacuuming, use of solvent, enzyme, or oxidizing cleaning agents, etc.) on reducing quantifiable histamine from common indoor surface via removal of bed bug feces from common indoor surfaces. The impacts of different flooring surfaces in the home have been examined for cockroach allergen concentrations (Cho et al., 2006) – this should be explored for bed bug histamine as well.

It will also be important to understand the impacts of professional bed bug control in different home environments on the longevity and stability of bed bug histamine. Histamine has been found to persist following successful eradication of bed bug infestations following heat treatment (DeVries et al., 2018). The impact of other traditional bed bug eradication methods such as liquid insecticide and dust application on histamine stability also merits exploration. In addition to the results of the present study, these future directions will be critical to the development of targeted bed bug histamine mitigation strategies.

Due to its fairly recent identification within homes (DeVries et al., 2018), histamine accumulation within the indoor environment has yet to be addressed. The detection of histamine from both infested and uninfested homes within our study suggests a "build-up" of histamine that persisted even after the bed bugs were eliminated/reduced. It is critical that future studies investigate the clinical relevance of bed bug histamine in conjunction with examination of resident cleaning practices and targeted bed bug mitigation strategies. While the medical relevance of chronic bed bug histamine exposure has yet to be characterized, histamine's role as a dustborne allergen that can spread beyond the bedroom epicenter bears further exploration.

Funding statement

This work was funded by the National Institutes of Health Director's Early Independence Award (DP5-OD028155 to ZCD) and a pilot grant to CS from the National Institute of Environmental Health Sciences of the National Institutes of Health (Award Number P30ES025128). CS was supported in part by the Blanton J. Whitmire Endowment. JMG was supported in part by scholarships from Pi Chi Omega, the Pest Management Foundation, and the Entomological Society of America. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Author contributions statement

CS and ZCD conceived and designed research. RGS, MG-M, MM, and ZCD collected samples and JMG analyzed samples. JMG and ZCD analyzed data. JMG wrote the initial draft of the manuscript. All authors contributed to critical revision of the manuscript. All authors read and approved the final manuscript.

Ethics approval statement

Institutional Review Boards (IRB) from North Carolina State University (#3840) and the University of Kentucky (#55949) approved this study. Before participation, adults (>18 years old) provided informed consent.

Data availability

Data are available in the supplementary materials

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We thank the residents who participated in this study and Simona Principato for assistance with calculating the method detection limits.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2023.163180.

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