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Nasal Trigeminal Perception of Two Representative Microbial Volatile Organic Compounds (MVOCs): 1-Octen-3-ol and 3-Octanol—a Pilot Study

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Abstract
Introduction Nasal symptoms can be associated with indoor mold overgrowth, even absent allergic sensitization. An alternative pathogenic mechanism—mucous membrane irritation by microbial volatile organic compounds (MVOCs)—has been proposed. We conducted a pilot human study of nasal irritation by two MVOCs, 1-octen-3-ol and 3-octanol, hypothesizing that the former would show greater irritant potency based upon the compounds' relative irritant potencies in rodents.
Methods Serial dilutions of the test compounds were prepared in odorless mineral oil vehicle, with headspace vapor concentrations documented by gas chromatography. Eight-step dilution series (with ascending concentration ratios ~ 1.34) were prepared. A nasal lateralization protocol was utilized. Ten subjects (seven females), aged 23–69, were each tested on four separate days, with each test compound being presented twice in alternating/counterbalanced order over the four testing days. Individual lateralization thresholds for a given compound, taken as dilution step, were averaged across subjects.
Results Eight subjects were reliably able to lateralize stimuli for one or both test compounds. Among the 32 testing sessions completed by these eight subjects, 1-octen-3-ol was successfully lateralized in 15/16 and 3-octanol in 11/16. The mean dilution step at threshold was 3.125 for 1-octen-3-ol and 2.58 for 3-octanol.
Conclusions When presented as brief (~ 4 s.) stimuli, high concentrations of identified MVOCs can act as nasal mucosal irritants. Both detectability and repeatability, but not absolute (ppm) thresholds, exhibited compound-specific trends consistent with animal experimental data. Studies involving more protracted exposures with larger sample sizes may yield more realistic irritant threshold estimates.
Implications At sufficiently high concentrations, MVOCs can produce nasal irritation in humans.

Keywords Fungi · Molds · Microbial volatile organic compounds (MVOCs) · Nasal irritation · Sensory irritation · Trigeminal irritation

Introduction

Microbial overgrowth—specifically, moisture-related fungal growth in building materials and furnishings—is an important public health concern. Indoor exposure to microbial products (including mold spores) is a confirmed risk factor for allergic sensitization, can trigger pre-existing rhinitis and asthma, and can result in other serious lung conditions such as hypersensitivity pneumonitis (Baxi et al. 2016; Bush et al. 2006). Beyond allergic conditions, microbially derived volatile organic compounds (MVOCs) have the potential to confer distinct sensory qualities to indoor air, including both a "musty" odor and—with sufficiently high exposure concentrations—sensory (eye, nose, and throat) irritation (Walinder et al. 2008).

MVOCs have been documented in field surveys of water-damaged buildings, and elevated MVOC levels (or mold-like

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odors) have been associated with various upper and lower respiratory tract health conditions (Araki et al. 2010, 2012; Elke et al. 1999; Jaakkola et al. 2013; Kawaguchi et al. 2014; Mendell et al. 2011; Schleibinger et al. 2005). Whether these associations represent a causal or "marker" role for MVOC exposures is a subject of debate. Although MVOCs' sensory irritation potential has been confirmed experimentally in animal bioassays (Korpi et al. 1999), few controlled human exposure studies have been conducted (Claeson et al. 2009; Ernstgard et al. 2013; Walinder et al. 2005, 2008). Because human sensory irritation thresholds have not been established for this class of compounds, interpretation of MVOC concentration samples taken from buildings with identified indoor air quality problems must be qualified by the relative lack of comparison data on the sensory potency of these compounds.

The current study was undertaken to utilize a rapid screening technique to compare the human sensory irritant potency of two representative MVOCs: 1-octen-3-ol and 3-octanol. We also compared these compounds' relative potency as human nasal irritants with their relative potency as "sensory irritants" in animal experimental studies. The strengths and limitations of this approach are discussed, as well as next steps in addressing uncertainties in this area of investigation.

Methods

Subject Recruitment

Subjects were recruited using flyers posted at a university campus and public health complex. Potential subjects were pre-screened via questionnaire. Inclusion criteria included age 18–70 and with or without a history of allergic or non-allergic rhinitis. Exclusion criteria included active tobacco smoking, a history of chronic sinusitis, nasal polyposis, angioedema or anaphylaxis, any chronic pulmonary or cardiac condition (e.g., asthma, chronic obstructive lung disease, coronary artery disease), or current pregnancy or lactation. Informed consent was obtained from all individual participants included in the study utilizing forms approved by both the University of California San Francisco (Committee on Human Research) and the California Health and Welfare Agency (Committee for the Protection of Human Subjects).

Stimulus Preparation

Chemosensory stimuli were prepared by serial dilution of food-grade 1-octen-3-ol (CAS No. 3391-86-4) and 3-octanol (CAS No. 589-98-0) (Sigma-Aldrich, St. Louis, MO) in 250-mL polypropylene "squeeze bottles" (Nalgene/Thermo Fisher Scientific, Rochester, NY), with a step-to-step liquid dilution ratio of 3:2. The diluent utilized was food-grade, light mineral oil (CAS No. 8042-47-5; Spectrum Laboratory Products, Gardena, CA). Twenty-four-step dilution sets were initially prepared with the goal of producing headspace vapor concentration ranges encompassing thresholds for both nasal trigeminal irritation and olfaction. Saturated vapor pressure for 23 °C was calculated for each compound utilizing the Antoine equation, with coefficients derived from a standard source (SaECaNet 2010; Yaws et al. 2005). Headspace concentrations of test vapors (as indexed by area under curve [AUC] relative to the undiluted specimen/saturated vapor pressure) were ascertained using an Agilent model 6850 gas chromatograph with gas sampling valve, non-polar megabore column, and flame ionization detector (FID) detector, with each headspace analysis done in triplicate.

For both compounds, headspace vapor from the maximally diluted specimens approached the limit of detection of the FID detector while still retaining a distinct odor. As a consequence, an initial goal of incorporating odor detection thresholds in the study procedure was deferred. Curvilinear deviations from ideal Henry's law relationships were apparent at lower [preliminary] dilution steps (i.e., higher concentrations), and hence, final dilution steps were chosen selectively to approximate a log-linear vapor dilution series incorporating the neat compound ("dilution 0") and seven dilution steps. The resulting dilution series thus differed in their highest concentrations (i.e., saturation vapor pressures): 895 ppm for 1-octen-3-ol and 565 ppm for 3-octanol. However, the mean step-to-step vapor ascending concentration ratios for the two dilution series were quite similar: 1.36 and 1.32, respectively (Figs. 1 and 2, Tables 1 and 2).

Experimental Design

The study consisted of a single-blinded, semi-randomized, sensory evaluation experiment. Each subject completed a total of four separate trigeminal irritant threshold testing sessions on four separate days: two for each for 1-octen-3-ol and 3-octanol. The two compounds were presented in alternating/counterbalanced order (in order to minimize stimulus-order effects), and each individual testing session occurred on a separate day (in order to minimize stimulus carryover effects). See Glossary—below—for precise definition of procedural terms.

Experimental Procedure

Trigeminal detection testing took place in a temperature-controlled facility (23 ± 1 °C) devoid of any extraneous auditory or visual stimuli. Testing was conducted using the lateralization technique (Lundstrom et al. 2012; Shusterman et al. 2003). For this technique, two squeeze bottles (identical-appearing stimuli and blanks with lateralization for each trial randomized using a computer-based program) were placed in

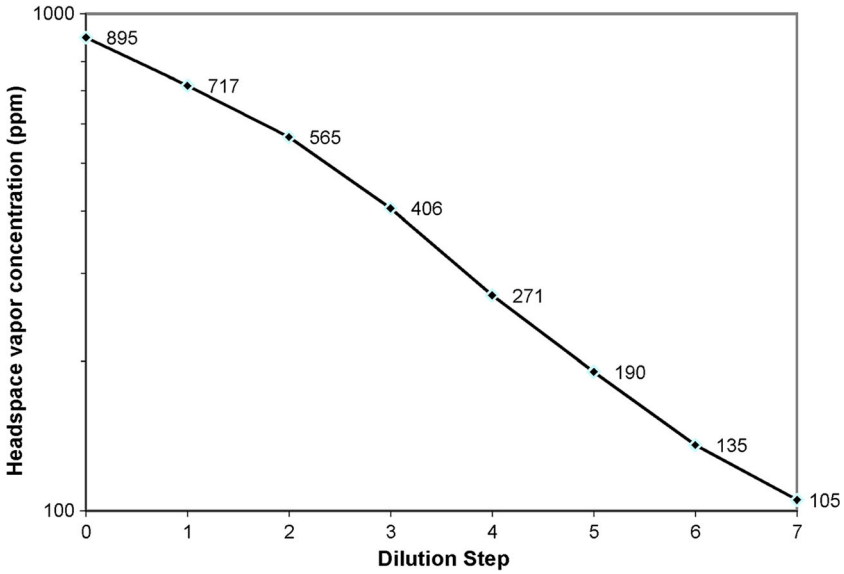

Fig. 1 Headspace vapor dilution curve for 1-octen-3-ol. Calculated saturation vapor pressure at 23 °C ("dilution step 0") is 895 ppm (see text)

a plastic holder, with the output of each bottle connected to the corresponding nostril via plastic tube and soft foam adapter (Fig. 3). At 60-s inter-trial intervals, the subject was instructed to "sniff" gently, and the two bottles were compressed simultaneously, with approximately 40 mL of headspace vapor delivered to each nostril over approximately 4 s. The subject was then instructed to indicate which side was "felt stronger" or "felt irritated." On an ascending concentration basis (i.e., beginning with the highest dilution step/lowest concentration) and with the constraint that there will be ≤ 3 active stimuli on each side, five identical stimulus pairs with laterality randomized by trial were evaluated for each concentration step, regardless of whether the laterality of the preceding trial was correctly identified. Immediately after indicating laterality, the subject was asked to rate (for the most affected side) the degree of nasal irritation ("tingling, stinging, burning, numbness, or cooling") using a computer-based visual analog scale (LabView; National Instruments, Austin, TX) calibrated using the labeled magnitude scale ("barely perceptible" to "strongest imaginable"—Green et al. 1996). The "trigeminal lateralization threshold" for each testing session was defined as the concentration step at which a subject first correctly localized the active stimulus on all five trials.

Statistical Analysis

Mean lateralization thresholds were computed both on an individual and group basis using the arithmetic mean dilution step (geometric mean % saturation and ppm headspace concentration) of successful lateralization determinations for each test compound. Percent correct lateralization and mean VAS ratings were tabulated for each [subject × compound × dilution

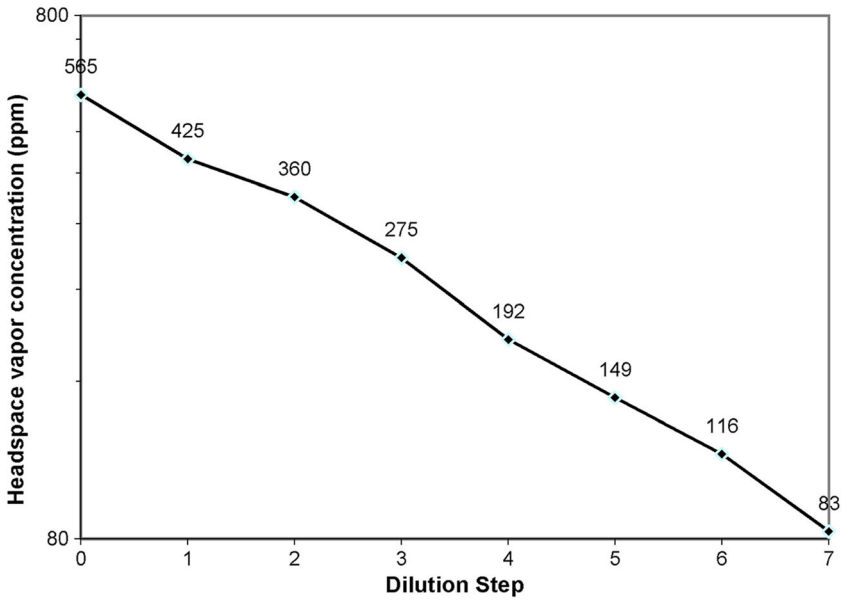

Fig. 2 Headspace vapor dilution curve for 3-octanol. Calculated saturation vapor pressure at 23 °C ("dilution step 0") is 565 ppm (see text)

Table 1 Headspace vapor concentrations and step-to-step vapor ascending concentration ratios for 1-octen-3-ol

Step	Concentration (ppm)	Ratio	% Saturation
0	895	1.25	100
1	717	1.27	80
2	565	1.39	63
3	406	1.50	45
4	271	1.43	30
5	190	1.40	21
6	135	1.29	15
7	105	1.00	12
		Mean ratio	
		1.36	

step] combination and were examined by analysis of covariance (ANCOVA). The numbers of successful lateralization determinations (contingency table) and distribution of individual lateralization thresholds for the two test compounds were examined by analysis of variance (ANOVA) using JMP Ver. 12 (SAS Institute, Cary, NC).

Results

Ten subjects—including seven females (and eight subjects free of rhinitis history), with a mean age of 40.8 years (range, 23–69)—were recruited and completed all four testing sessions. Accordingly, a total of 20 threshold tests were completed for each compound. Eight of the 10 subjects were able to lateralize one or both stimuli in at least one threshold test each, and subsequent analysis was limited to the 32 threshold tests completed by these 8 subjects. Successful lateralization for the criterion number of repetitions (five) occurred in 15 of 16 tests (94% of tests) in eight subjects for 1-octen-3-ol and in 11 of 16 tests (69% of tests) in six subjects for 3-octanol (r^2 = 3.28;

Table 2 Headspace vapor concentrations and step-to-step vapor ascending concentration ratios for 3-octanol

Step	Concentration (ppm)	Ratio	% Saturation
0	565	1.33	100
1	425	1.18	75
2	360	1.31	64
3	275	1.43	49
4	192	1.29	34
5	149	1.28	26
6	116	1.41	21
7	83	1.00	15
		Mean ratio	
		1.32	

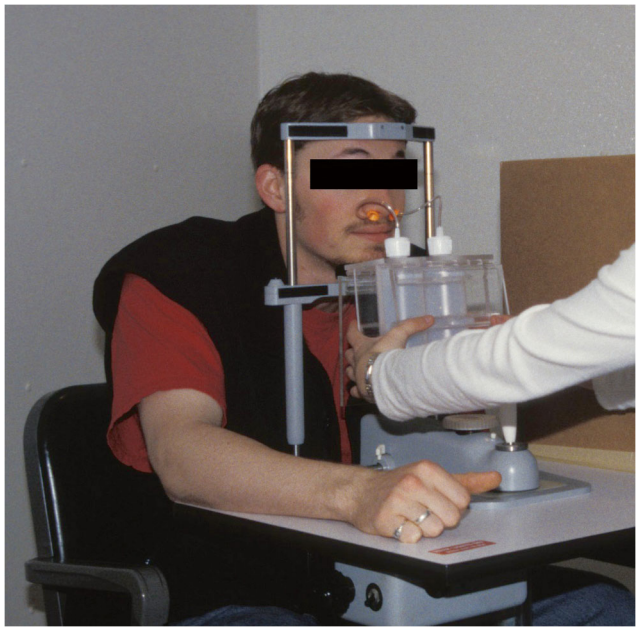

Fig. 3 Testing apparatus for nasal trigeminal lateralization (see text for details)

p = 0.07; Fisher exact = 0.09). Lateralization thresholds showed significant individual repeatability for 1-octen-3-ol (r^2 = 0.74; $p < 0.05$) but not for 3-octanol (r^2 = 0.08; p = 0.65). As illustrated in Fig. 4, the mean dilution step at threshold was 3.125 for 1-octen-3-ol (40.1% of saturation vapor pressure) and 2.58 for 3-octanol (52.4% of saturation vapor pressure—differences not statistically significant). Based on these data, the estimated lateralization thresholds for brief (~ 4 s.) exposures were 359 ppm for 1-octen-3-ol and 296 ppm for 3-octanol (difference not statistically significant).

Individual subjects' linearized responses for mean detection fraction (i.e., proportion of trials with correct lateralization) as a function of dilution step appear in Fig. 5a (for 1-octen-3-ol) and in Fig. 5b (for 3-octentol). Similarly, mean VAS ratings of subjective nasal irritation are modeled by dilution step in Fig. 6a (for 1-octen-3-ol) and in Fig. 6b (for 3-octentol). Using analysis of variance for unequal slopes, inter-subject differences were statistically significant (i.e., $p < 0.05$ or lower) for all but 3-octanol detection (Fig. 5b). Similarly, increasing stimulus concentration (decreasing dilution step) was a significant determinant of all outcomes except for VAS nasal irritation rating of 1-octen-3-ol (Fig. 6a). Smoothed (non-linear) functions for raw data (detection fractions and VAS ratings) are posted for visual inspection as supplemental material at https://www.ocf.berkeley.edu/~dshuster/MVOC-Sensory/MVOC_Sensory_Supplemental_Material.pdf.

Discussion

Two representative C-8 MVOCs, presented as brief (~ 4 s) stimuli, elicited subjective nasal irritation in the majority of

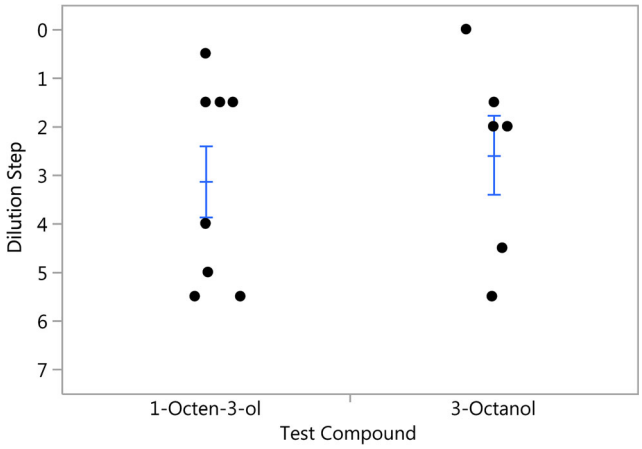

Fig. 4 Distribution of individual subjects' dilution steps at lateralization threshold (mean ± standard error). Each observation represents the arithmetic mean of two threshold determinations in five of the six subjects who successfully lateralized 3-octanol and in seven of the eight individuals who successfully lateralized 1-octen-3-ol. The remaining two observations represent single successful lateralization tests each

test subjects sufficient to yield lateralization thresholds. Based on a limited sample size, the relative potency of the two test compounds did not differ significantly, although a statistically non-significant trend was observed toward greater detectability when comparing 1-octen-3-ol with 3-octanol (p = 0.07).

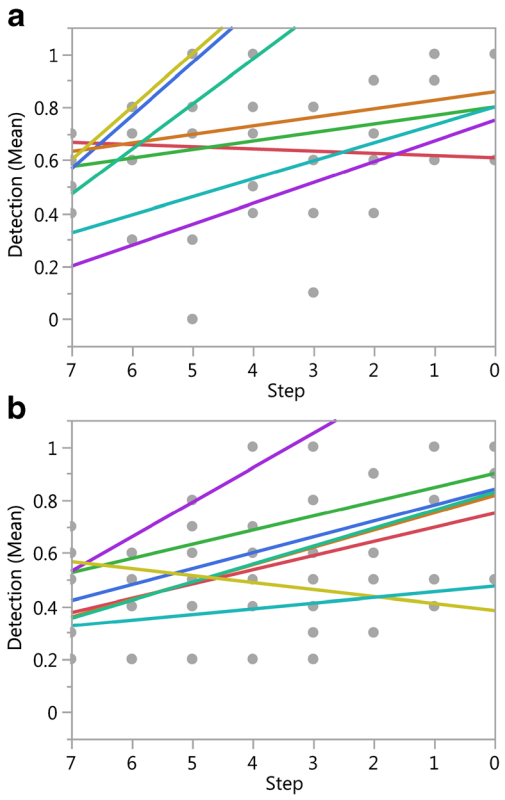

Fig. 5 Linearized relationships (ANCOVA) between detection fraction (0–1) and dilution step (7 to 0) for **a** 1-octen-3-ol and **b** 3-octanol for subjects who successfully lateralized at least one set of five trials on at least one of the two test compounds

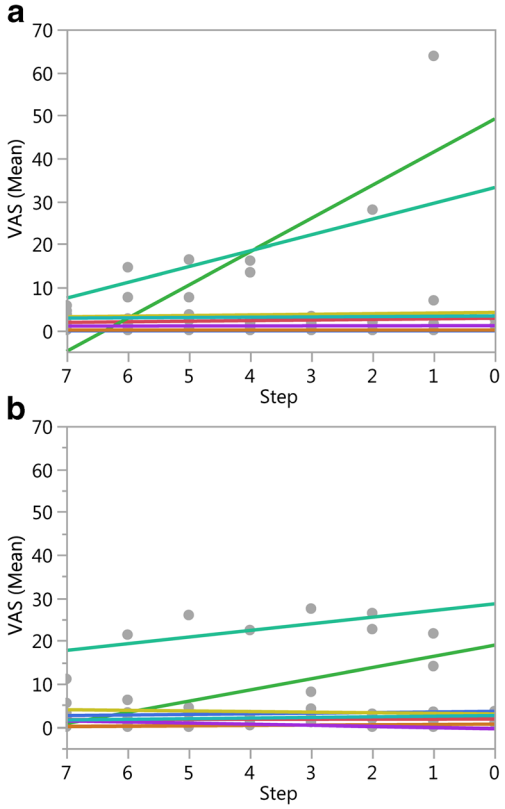

Fig. 6 Linearized relationships (ANCOVA) between visual analog rating of subjective nasal irritation (0–100) and dilution step (7 to 0) for **a** 1-octen-3-ol and **b** 3-octanol for subjects who successfully lateralized at least one set of five trials on at least one of the two test compounds

Although the mean dilution step at detection was higher (and % saturation vapor pressure lower) for 1-octen-3-ol than for 3-octanol, allowing for the compounds' differing saturation vapor pressures, the estimated mean lateralization threshold was actually higher for 1-octen-3-ol than for 3-octanol (NS).

On analysis of covariance, linearized detection probability functions (proportion of trials with correct lateralization) for both test compounds showed significant stimulus concentration effects, with detection fraction generally rising with stimulus concentration (Fig. 5a, b). Subjectively, the majority of subjects reported only "barely perceptible" or "weak" nasal irritation over the course of their testing sessions (Fig. 6a, b). Both of these observations are reassuring in terms of the underlying validity of the localization procedure as a threshold measure of subjective nasal irritation.

Our expectation that 1-octen-3-ol would be a more potent irritant than 3-octanol was based on several lines of evidence. Utilizing the so-called Alarie assay for sensory irritant-induced respiratory slowing in rodents (Alarie 1966; ASTM 1984), Korpi et al. (1999) found the "RD_{50}" (concentration leading to a 50% reduction in respiratory rate) was lower for 1-octen-3-ol (35 ppm) than for 3-octanol (256 ppm). Since the

RD_{50} has been shown to relate to minimum irritant concentrations observed in controlled human exposure studies, interspecies extrapolation from the RD_{50} seemed warranted (Kuwabara et al. 2007).

Epidemiologically, in selected field studies, indoor air concentrations of 1-octen-3-ol (but not 3-octanol) have been predictive of upper airway symptoms, including mucous membrane irritation and allergic rhinitis (Araki et al. 2010, 2012). In the single controlled human exposure ("chamber") study involving 1-octen-3-ol exposure (10 mg/m^3 [or 2 ppm] times 2 h), moderately strong subjective nasal irritation—increasing in intensity with increasing exposure duration—was reported on VAS (Walinder et al. 2008). Concentrations documented in recent field settings, by contrast, are generally quite low in comparison to either the Walinder study or ours, ranging in homes up to ~ 0.3–1.6 ppb (Schleibinger et al. 2008; Araki et al. 2010, 2012) and in schools up to ~ 40 ppb (Kim et al. 2007). However, individual MVOC compounds do not occur in isolation, and combinations of MVOCs have shown a supra-additive upper respiratory irritation effect in an animal model (Korpi et al. 1999).

An immediately obvious difference in comparing our 1-octen-3-ol results with that of Walinder et al. (2008) was the high vapor concentration necessary to produce lateralization in a 4-s exposure (i.e., ~ 360 ppm) compared to that producing subjective nasal irritation over a 2-h period (~ 2 ppm). One obvious explanation involves exposure duration, a variable dealt with by "Haber's law." The simplest form of Haber's law asserts that, for a given toxicologic endpoint, concentration (c) and time (t) will vary reciprocally across experimental conditions (i.e., $c \times t$ = constant). Utilizing this model, the expected concentration difference in comparing a 4-s with 2-h exposures would be 1800-fold. Instead, the two experiments differed in concentration by approximately 180-fold, consistent with the following: (1) Walinder et al. exposed subjects to levels in excess of 1-octen-3-ol's [2-h] nasal irritation threshold and (2) a more complex version of Haber's law may apply in this situation. Supporting these points, the fact that the mean VAS rating at the end of 2-h exposure to 2 ppm was 37 on a scale of 0 to 100 (i.e., moderately strong) indicates that the Walinder experiment was conducted well into the supra-threshold range, making the results not directly comparable to a threshold determination. Regarding the Haber's law formulation, analysis of human sensory irritation data suggests that minimally irritating concentrations do not decrease in direct proportion to increasing exposure time, but rather follow an exponentiated relationship ($c^n \times t$ = constant) (Shusterman et al. 2006). Thus, some combinations of these two factors (as well as some degree of intra-nasal dilution due to the act of "sniffing") likely explain the difference in the two irritant potency estimates for 1-octen-3-ol.

In terms of limitations, this was a "pilot study" of a rapid screening technique, with limited statistical power. Further, a potential downward bias in our results derived from the fact that, for those subjects who had "non-detect" threshold tests (i.e., failed to identify laterality on all given trials at dilution step 0) for a given test compound, these tests were omitted from the threshold analysis (rather than tabulating them using arbitrarily high surrogate threshold concentrations). Finally, chamber studies involve normal breathing patterns without terminal dilution of stimuli and by simultaneously stimulating trigeminal nerve endings in the eyes, nose, and throat produce "spatial integration" of stimuli, generally yielding lower threshold values. While mathematical modeling may help fill the conceptual gap between rapid experimental techniques and real-life conditions, more protracted (and realistic) exposure conditions are desirable if one is to extrapolate to environmentally realistic exposure conditions.

An alternative approach to estimating human sensory irritation thresholds to MVOCs would involve conducting repeated chamber studies of self-rated sensory irritation—with each experimental arm thereof requiring a minimum of approximately 3 h of subject participation—at a range of different concentrations, including "sham" [clean air] exposure. Such studies would generate lowest observed adverse effect levels (LOAELs) as sensory irritation threshold approximations. By contrast, since lateralization testing sessions can yield individual threshold estimates in approximately an hour's time, lateralization might, if validated with appropriate extrapolation models, offer a means of prioritizing potential test compounds (and quantitatively "ranging" exposures) for more resource-intensive chamber studies. Some combination of screening and chamber studies may be useful in characterizing the sensory irritant potential of multiple MVOCs under more environmentally realistic exposure conditions. Subsequent comparison of sensory irritation threshold estimates from multi-hour chamber studies vs. air sampling measurements from water-damaged ("problem") buildings might help address the issue of MVOCs' direct (as opposed to marker) role in explaining mucous membrane/respiratory tract symptoms.

Finally, prediction of VOCs' sensory irritation potency has been approached using structure-activity (or "*in silico*") methods. Investigators at the University of California, San Diego, in collaboration with University College London, have derived empirical formulae modeling sensory irritation potency based on volatile compounds' physicochemical properties and calibrated the predictions of these models against psychophysical testing results from a variety of homologous series, including alcohols, ketones, aldehydes, esters, carboxylic acids, terpenes, and alkylbenzenes (Cometto-Muñiz et al. 2010; Abraham et al. 2016). To our knowledge, the vast majority of compounds classified as MVOCs (including 1-octen-3-ol and 3-octanol) have yet to be evaluated using these

models. Were we to have both sensory testing and physicochemical data for at least three different MVOCs, the possibility would arise of testing the predictions of one or more regression models for the *relative* sensory irritant potency of these target compounds.

Conclusions

MVOCs have been documented at elevated levels when comparing water-damaged and non-water-damaged buildings. In some field studies, MVOCs have been associated with mucous membrane and/or lower respiratory tract health complaints. Limited data exist on the sensory [mucous membrane] irritant potential of this large and diverse class of compounds. The use of rapid screening tests (such as nasal lateralization) may assist in prioritizing MVOCs for more resource-intensive human sensory irritation studies.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Glossary

Inter-test interval	The minimum time allowed between successive threshold tests (at least 1 day)
Inter-trial interval	The time allowed between successive trials (nominally, 60 s)
Lateralization threshold	For a given test compound, the average (ascending concentration) step at which an individual successfully lateralizes stimuli on five successive trials
Step	Stimulus dilution step (0 = most concentrated; 7 = most dilute)
Stimulus order:	
Alternating	i.e., “1212” vs. “2121”
Counterbalanced	Half of subjects with each of two alternating stimulus orders
Threshold test	The entire testing procedure for a given day, incorporating five trials at each (ascending concentration) step until five of five are correctly lateralized
Trial	The simultaneous presentation of a stimulus and blank stimulus to opposite nostrils, with randomized lateralization
VAS	Visual analog scale [rating of subjective nasal irritation]

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