Title

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Publication Date

1993

Data Availability

The data associated with this publication are within the manuscript.

Peer reviewed

Indoor Air '93 (Proceedings of the 6th International Conference on Indoor Air Quality and Climate): Indoor Air'93, Helsinki, Vol. 1, Health Effects, pp. 561-566, 1993

NASAL IRRITATION AND ODOR FROM HOMOLOGOUS SERIES OF CHEMICALS

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ABSTRACT

To assess the independent contribution of nasal irritation (pungency) and odor to the detection of nonreactive volatile organic compounds (VOCs), we measured nasal detection thresholds in subjects lacking olfaction (anosmics) and in matched controls (normosmics). Homologous alcohols, acetates, and ketones served as stimuli. Most substances evoked irritation (i.e., were detected by the anosmics). Both odor and pungency thresholds decreased with carbon chain length. A robust linear correlation, with slope close to one, between nasal pungency and saturated vapor concentration for all stimuli together suggests that irritation from nonreactive VOCs relies on a broadly tuned physicochemical interaction with a susceptible biophase.

INTRODUCTION

Polluted indoor environments often generate complaints of sensory irritation and odor (e.g., see [1]), as well as of non-specific neurological symptoms (e.g., headache, difficulty in concentration, tiredness, lassitude). Among all these, sensory irritation and odor are probably the most amenable to quantification.

In humans, two sensory systems convey information on the presence of airborne chemicals: olfaction and the so-called common chemical sense (CCS) [2]. Specific anatomical structures: the olfactory neurons of the olfactory epithelium, located on the upper part of the nasal cavity, give rise to odor sensations. The axons of these neurons constitute the olfactory nerve (Cranial Nerve I) which carries the odor message to the olfactory bulb and to higher levels of the central nervous system. Recent studies support the existence of specific olfactory receptors in the cilia of the olfactory neurons [3].

Common chemical sensations are much more widespread. They arise in all mucosae (ocular, nasal, oral, respiratory, genital and anal), as well as in the skin, underneath the epidermis [4]. In the particular case of the face mucosae, free nerve endings of the trigeminal nerve (Cranial Nerve V) mediate common chemical sensations. These sensations comprise: prickling, piquancy, burning, irritation, tingling, freshness and stinging, among others. We refer to them collectively as **pungent** sensations.

Since these two chemical senses respond virtually to the same compounds, it has been difficult to study them independently in humans. It is generally true that at low concentrations odor predominates and at high concentrations pungency predominates [5, 6]. Nevertheless, the basic question remains: where does the CCS start to kick in? A mutual interaction observed

between perceived odor and pungency, by which pungency inhibits odor markedly and odor inhibits pungency slightly [7], can further obscure the independent contribution of olfactory and CCS responses.

An effective way to address the problem has entailed the use of subjects lacking a functional sense of smell, i.e., anosmics [8, 9] and subjects with unilateral destruction of the trigeminal nerve [10]. The former provide judgments of nasal pungency unbiased by odor sensations, and the latter provide judgments of odor intensity without the trigeminal response. The proliferation in the last ten to fifteen years of taste and smell clinics, and the development of standardized olfactory tests (e.g., [11-13]) increased the availability of anosmic patients with a documented clinical history.

Our approach combines the use of anosmics and normosmics (i.e., persons with a normal sense of smell), the measurement of nasal detection thresholds with a uniform methodology, and the use of selected chemical stimuli (typically homologous series, where physicochemical properties change systematically). We assume that a threshold nasal sensation elicited by an airborne substance in a normosmic subject reflects only odor. Moreover, we know that a threshold nasal sensation elicited in a clinically anosmic patient can only reflect pungency (or CCS stimulation). The study of how odor and pungency thresholds vary in homologous chemical series reveals: first, the concentrations at which each member starts to elicit odor and starts to elicit pungency, and, second, how systematic changes in molecular structure affect the relative efficacy of compounds to elicit these two sensations.

The investigation of a number of such series probes the role of physicochemical parameters in the production of odor and pungent sensations. Here we present the results of measuring olfactory and nasal CCS thresholds for homologous alcohols [14], acetates [15], and ketones [16], as well as for some secondary and tertiary alcohols and acetates. For selected acetates we also measured eye irritation thresholds.

MATERIALS AND METHODS

Stimuli. All substances employed were analytical-grade reagents. The alcohols included: methanol through 1-octanol, 2-propanol, 2-butanol (sec butyl alcohol), 2-methyl-2-propanol (tert butyl alcohol), and 4-heptanol. The acetates included: methyl through octyl acetate, decyl acetate, dodecyl acetate, sec butyl acetate, and tert butyl acetate. The ketones comprised: 2-propanone (acetone), 2-pentanone, 2-heptanone, and 2-nonanone. Deionized water served as the solvent for methanol, ethanol, 1-propanol, and 2-propanone. Mineral oil served as the solvent for all the rest.

Dilution series were prepared for each stimulus, starting with the pure compound (100% v/v), labeled dilution step 0. Successive dilutions comprised up to dilution step 15. Typically each step represents a three-fold dilution. Stimuli were presented in 250-ml capacity, squeezable, polyethylene or polypropylene bottles [17], each containing 30 ml of solution. The bottle closure had a pop-up spout that allowed testing each nostril separately [18]. To measure eye irritation thresholds, the same bottles were used. In this case, the top of the bottle contained a 25-ml roughly conical reservoir chamber the rim of which was placed around the eye. A squeeze of the bottle delivered a puff of vapor directly to the eye. The vapor concentration in the headspace of each bottle was measured by gas chromatography (photoionization detector), using a gas-sampling valve. For every substance, chromatographic readings were taken from the headspace of each bottle in the series, including the bottle containing saturated vapor at room temperature

(23 °C). The concentration corresponding to saturated vapor for each compound is known from handbooks or databases on physical properties. Knowledge of the concentration of saturated vapor and its associated chromatographic reading allowed conversion of the readings from the other bottles into concentration units, and a calibration curve was derived.

Subjects. Typically a total of eight subjects participated in the evaluation of each chemical series. Half of them were clinical anosmics (patients from the Connecticut Chemosensory Clinical Research Center, University of Connecticut, or Yale-New Haven Hospital) as determined by the CCCRC olfactory test [18]. The other half were age-, gender-, and smoking status-matched normosmics. The anosmic group employed in the study of each series included congenital and head trauma anosmics. Subjects tested for eye irritation were normosmics.

Procedure. Participants delivered the stimulus and blanks (water or mineral oil) to themselves by placing the pop-up spout inside the designated nostril and squeezing the bottle as they sniffed. They rapidly learned to squeeze and sniff with constant vigor across trials. In the case of eye irritation testing, subjects placed the rim of the reservoir around the eye and squeezed the bottle while keeping the tested eye open.

The method employed was a two-alternative, forced-choice, ascending method of limits. Briefly, the subject started by using one nostril or eye to compare the intensity of the lowest concentration of a substance (e.g., dilution step 15) to a blank and deciding (forced-choice) which one was stronger. A correct choice led to the presentation of the same concentration (from another bottle) also paired with a blank. An incorrect choice led to the presentation of the next dilution step (a concentration three times higher: ascending method of limits, e.g., dilution step 14) paired with a blank. This continued until five correct choices were made in a row, in which case that step was taken as the threshold. The same procedure was then repeated with the other nostril or eye. After that, testing began with another substance in the series in identical manner. The ascending concentration approach to the threshold and the alternate use of each nostril helped to minimize the effects of the commonly found phenomenon of olfactory adaptation (e.g., [19]).

In the case of nasal testing, sessions lasted between two and three hours. They were repeated until 12 thresholds (6 for each nostril) per subject were obtained for each compound. In the case of eye irritation testing, sessions lasted between 15 and 45 min and were repeated until 6 thresholds (3 for each eye) per subject per compound were obtained. The order of presentation of the chemicals within each series differed from subject to subject. The number of times that the right or left nostril (or eye) was tested first for a certain substance was counterbalanced for each subject.

Data analysis. The individual thresholds for each participant, expressed as dilution steps, were averaged. These averages were then converted to headspace concentrations (ppm) with the gas chromatography-derived calibration curve. Finally, thresholds (in ppm) were averaged geometrically across subjects in each group (anosmic and normosmic).

RESULTS

Figure 1 shows nasal pungency (irritation) thresholds – obtained from anosmics – and odor thresholds – obtained from normosmics – for each of the chemical series. As expected, normosmics outperformed anosmics at detection of all stimuli. For all series, odor and pungency

thresholds decreased with increasing carbon chain length. Nevertheless, considering only the first 4 to 7 members of each series, the rate of decline of odor thresholds was steeper than that of pungency thresholds.

Interestingly, anosmics not only detected the lower members of each series (e.g., methanol, methyl acetate, 2-propanone) – compounds traditionally considered irritants – but also the higher members (e.g., heptanol, heptyl acetate, 2-nonanone) – compounds not often considered irritants. Furthermore, the absolute pungency threshold of the latter (in ppm) was two or more orders of magnitude below that of the former. This indicates that the high molecular weight, low vapor pressure substances are definitely able to evoke nasal pungency, and that they do it at substantially lower airborne concentrations than their low molecular weight, high vapor pressure counterparts. Only four of all compounds tested failed to be detected at all by one or more of the anosmics. These were: 1-octanol, and octyl, decyl, and dodecyl acetate.

For the alcohols, changing the OH functional group from a primary carbon to a secondary carbon always increased both odor and pungency thresholds (1-propanol vs. 2-propanol, 1-butanol vs. 2-butanol, 1-heptanol vs. 4-heptanol, see Figure 1). Changing the OH to a tertiary carbon further increased both types of thresholds (1-propanol vs. 2-methyl-2-propanol, see Figure 1).

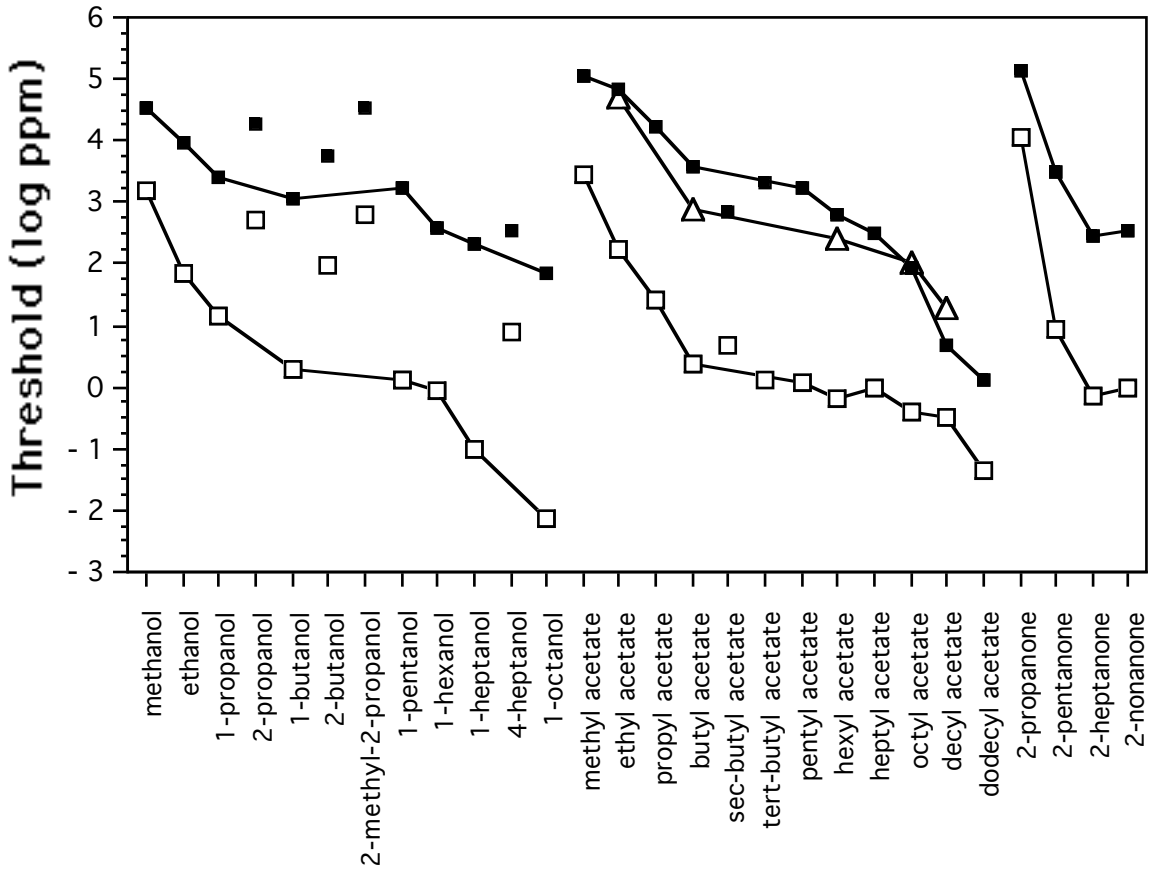

Fig. 1. Thresholds for nasal pungency (filled squares), odor (empty squares) and eye irritation (triangles). Only n-members of the series are joined by a line.

For the acetates, branching the main carbon skeleton failed to produce impressive changes in odor or pungency thresholds (butyl acetate vs. sec-butyl acetate, butyl acetate vs. tert-butyl acetate, see Figure 1). Sec-butyl acetate displayed a slightly lower pungency threshold and a slightly higher odor threshold than butyl acetate.

Eye irritation thresholds for selected acetates fell close to nasal pungency thresholds. Decyl acetate evoked eye irritation in only one of the four participants in the experiment.

Figure 2 depicts the individual thresholds for the acetates in the two groups of subjects. As exemplified by the figure, the group results presented in Figure 1 are not an artifact of averaging since anosmics and normosmics show no overlap, and all subjects in each group conform to a common trend.

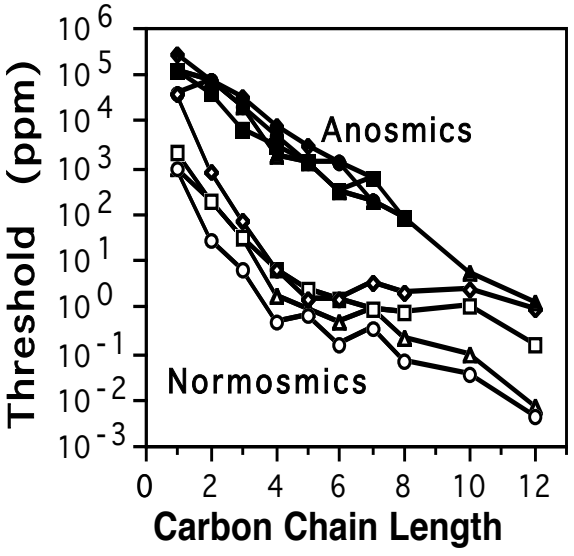

Fig. 2. Individual nasal thresholds for a group of four anosmics and a group of four matched-normosmics, using a homologous series of acetates (methyl=1 through dodecyl=12 acetate) as stimuli.

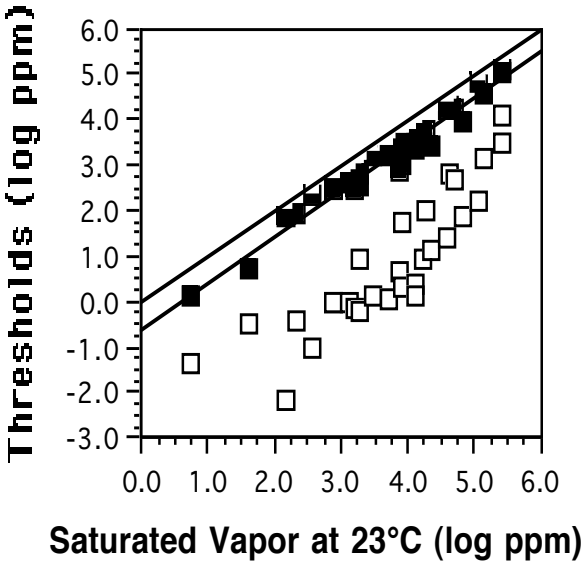

Fig. 3. Pungency (filled squares) and odor (empty squares) thresholds for all chemicals studied as a function of saturated vapor concentration at room temperature. The saturated vapor identity line (slope=1.00. r=1.00, no symbols) is shown for reference. The function for pungency has a slope=1.02 and r=0.98.

DISCUSSION

In order to gain insight into how well general physicochemical properties can explain the sensory thresholds obtained, we plotted all thresholds as a function of saturated vapor concentration at room temperature (Figure 3).

In the logarithmic coordinates of the figure, pungency thresholds for the three homologous series conform well to a common linear function. Moreover, this nasal pungency function closely parallels the saturated vapor identity line (slope=1.00 and r=1.00). Thus, the pungency of these substances arises, in the absence of the sense of smell, at an approximately constant percentage of saturated vapor (≈32%) irrespective of the functional group or carbon chain length of the stimulating molecule. This outcome supports the notion that simple physical properties could predict the level at which nonreactive airborne chemicals can elicit nasal pungency.

Figure 3 reveals that odor thresholds fail to show the uniform relationship with saturated vapor concentration seen for pungency. This presumably indicates that the sense of smell is more finely tuned to the molecular features of stimulating molecules than is the CCS.

The present results indicate that the higher members of the various nonreactive homologous chemical series evoke nasal pungency at concentrations below that of the more volatile lower members. They also suggest that irritation rests heavily on a nonspecific physicochemical interaction between airborne molecules and a susceptible biophase, most likely within the lipophilic environment of cell membranes.

What are the implications for indoor air quality of these studies probing into the basic stimulus-response properties of the human common chemical and olfactory senses? From one perspective, the use of anosmics has allowed to gain insight for the first time into the production of nasal irritation in the absence of olfaction. Systematic testing of homologous series of nonreactive chemicals (many of them commonly present indoors, see [20]) will eventually allow the development of quantitative structure-activity relationships (QSARs) for pungency (sensory irritation) in humans. So far such QSARs have relied exclusively on animal data [21].

From another perspective, if nasal pungency from nonreactive chemicals is broadly tuned to the molecular features of the stimuli, one would expect that the effects of a wide variety of volatile organic chemicals (VOCs) will exhibit considerable sensory additivity. Perhaps this can explain the appearance of sensory irritation in indoor environments where dozens of VOCs are simultaneously present albeit at concentrations too low to be responsible individually for the observed sensory effects. In this regard, we are beginning to address the issue of how anosmics and normosmics respond to mixtures of VOCs.

ACKNOWLEDGEMENTS

This work was supported by NIH Grant DC00284.

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