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Trigeminal and Olfactory Sensitivity: Comparison of Modalities and Methods of Measurement

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Abstract

Objective: The principal objective was to chart sensitivity for human nasal irritation by alternative psychophysical methods, a common detection procedure vs. a nasal lateralization procedure that required the subject to indicate whether a vapor had stimulated the left or right nostril. This objective relates to the broader issues: a) whether subjects with normal olfaction (normosmics) can yield, through novel methodology, an index of sensitivity to nasal irritation comparable to that obtained from subjects without olfaction (anosmics) and b) whether both types of subjects have similar irritation sensitivity in general. This study sought to gauge interconvertability both between types of subjects and between modes of stimulus presentation, for irritative and, where appropriate, olfactory stimulation.

Methods: Static dilution series of four n–aliphatic alcohols, chosen to represent volatile organic compounds (VOCs), provided the source of calibrated olfactory and irritative vapors, emitted from their squeezable containers into the nose or eye by either a mechanical device or by hand. Standard psychophysical methodology (forced–choice; ascending strength of stimulation) served to chart detection thresholds for irritation and odor and an analogous procedure served to chart the threshold for localization of stimulation.

Results: Within the limits of resolution, detection thresholds and nasal localization thresholds yielded comparable indices of the potency of the VOCs to evoke nasal irritation. The thresholds agreed well with those for detection of eye irritation, though only the eyes proved able to detect irritation from 1–octanol. The method of emitting the stimulus had little material effect on measures of either irritative or olfactory detection.

Conclusions: The threshold for nasal localization offers a suitable way to measure nasal irritation in normosmic persons. Olfactory stimulation does not interfere with the measure since subjects cannot localize on that basis. Anosmic and normosmic persons have comparable sensitivity to nasal and ocular irritation. If anosmic persons have any lower sensitivity, as sometimes claimed, it would seem to have only trivial consequences for estimates of the irritative potency of VOCs.

Key words: Smell — Nasal Irritation — Eye Irritation — n–Alcohols — Anosmia

Introduction

Many, or perhaps even most, volatile organic compounds (VOCs) can elicit odor sensations at relatively low concentrations and pungency at higher concentrations. The concentration at which the detection of pungency just begins has proven difficult to specify in subjects who have normal olfaction. The presence of odor sensations apparently interferes with the measurement, presumably because of ambiguity regarding when an odor itself becomes an irritation and when the sensation takes on a pungent character that represents the recruitment of chemesthesis via stimulation of the trigeminal nerve. Specification of the detection threshold for pungency has proven straightforward, however, in subjects who lack a sense of smell. Anosmic subjects have consistently yielded thresholds with little intersubject variability, far less than that shown by normosmics for odor detection (Cometto–Muñiz and Cain 1990, Cometto–Muñiz and Cain 1991, Cometto–Muñiz and Cain 1993, Cometto–Muñiz and Cain 1994b, Cometto–Muñiz et al. 1997a, Cometto–Muñiz et al. 1997b). The data from small samples of anosmics per study over a number of studies have permitted derivation of a physicochemical model to predict thresholds for pungency with high certainty (Abraham et al. 1996). Despite the success of the studies of anosmics, it remains of interest to specify odor thresholds and pungency thresholds in the same individuals (viz., normosmics). The present study reëxamines this issue via the psychophysical measurement of nasal localization or, more precisely stated, nasal lateralization.

Studies of odor and pungency thresholds from this laboratory have employed chemicals from homologous series (viz., alcohols, acetate esters, ketones, alkylbenzenes, aliphatic aldehydes, carboxylic acids). Since physicochemical properties in such series change regularly, these substances provide a "benchmark unit" (i.e., carbon chain–length) against which to measure potency of odor, nasal pungency, and eye irritation, another chemesthetic response to VOCs (Cometto–Muñiz and Cain 1991, Cometto–Muñiz

and Cain 1995b). A solvation equation that combines four physicochemical parameters has served well to describe and predict the nasal pungecny potency, for single–sniff exposures, of more than 40 such VOCs of various chemical functionalities (Abraham et al. 1996, Cometto–Muñiz et al. 1997a).

Three decades ago, von Békésy argued that nasal localization (lateralization) could occur in olfaction via internostril time– and intensity–disparities in stimulation (von Bèkesy 1964). His stimuli may, however, have had considerable chemesthetic impact. Other investigations have concluded that localization may occur only via chemesthesis, and not olfaction (Kobal et al. 1989, Schneider and Schmidt 1967). This outcome suggested the possibility that when a vapor can just be lateralized, it has just reached the threshold of true pungency in either the anosmic or the normosmic subject. If so, then threshold for lateralization could serve as a surrogate for the threshold for chemesthesis. Studies with the relatively odorless chemesthetic stimulus carbon dioxide have endorsed this view (Wysocki et al. 1992), as has preliminary work on VOCs from this laboratory (Cain and Cometto–Muñiz 1996).

The present investigation continues the thematic approach to the determinants of olfaction, and nasal and ocular chemesthesis in homologous series. The work entailed measurement of: 1) nasal pungency thresholds in anosmics, 2) odor thresholds in normosmics, 3) nasal localization thresholds in anosmics and normosmics, and 4) eye irritation thresholds in anosmics and normosmics for n–aliphatic alcohols.

<center>Materials and Methods</center>

<u>Subjects.</u> The anosmic group comprised five subjects: three males and two females. The males included a 57 year–old, nonsmoking congenital anosmic; a 42 year–old, cigarette smoking head–trauma anosmic; and a 41 year–old, nonsmoking idiopathic

anosmic. The two females were 36 and 38 year-old nonsmoking congenital anosmics. This group gave thresholds for nasal pungency, nasal localization, and eye irritation.

The normosmic group comprised four subjects: three males and one female. The males were 57, 36, and 36 years old, all nonsmokers. The female was a 36 year-old nonsmoker. This group gave thresholds for odor, nasal localization, and eye irritation.

The protocol for the study was approved by the Human Subjects Committee of the University of California, San Diego. Subjects gave written consent before participation.

Stimuli. The homologous n-alcohols tested included: 1-propanol, 1-butanol, 1-hexanol, and 1-octanol. 1-Propanol was 99%+ pure, and all other compounds met specifications in the Food Chemicals Codex (FCC). Starting with undiluted chemical, dilution series were prepared in quadruplicate for each substance in ternary dilution steps. Undiluted chemical was labeled dilution step 0 (100% v/v); following it were dilution steps 1 (33.3% v/v), 2 (11.1% v/v), 3 (3.7% v/v), etc. Distilled water served as solvent for 1-propanol, and light mineral oil (FCC grade) served as solvent for the other compounds.

The four identical dilution series for each chemical were presented to the subjects in 270-ml polypropylene squeeze-bottles (Cain 1989) containing 30 ml of solution. For testing odor and nasal pungency, the bottles had a cap with a pop-out spout that could fit into one nostril. This allowed testing each nostril separately. For testing eye irritation, the bottles had a cap of the sort used with variable volume dispensers (see Cometto-Muñiz and Cain 1991). A tube through the cap connected the headspace of the bottle to a conical 25-ml reservoir, the rim of which fitted around the

eye. A squeeze of the bottle sent the puffed vapor from the headspace to the reservoir where the eye was exposed. The apparatus allowed separate testing of each eye.

Concentration of the headspace of every bottle was measured at the time of preparation. Thereafter, alternately selected odd and even dilution step bottles from each of the quadruplicate sets were checked three or four times during the study to assure stability. Measurements were made directly on the headspace of the bottles via a gas chromatograph (FID detector) equipped with a gas sampling valve (1-ml sampling loop). The average reading made from the bottles containing each undiluted substance (100% v/v) was assumed to correspond to saturated vapor of the substance at room temperature (≈23°C). Concentration of such saturated vapor (in ppm) was derived from data on vapor pressure listed in handbooks and databases. Concentration of all other bottles was referred to that of the saturated vapor.

Apparatus. As explained below, the squeezing of the bottles was accomplished through hand squeezing or mechanical squeezing. The mechanical squeezer consisted of an acrylic frame that held two bottles in place. When the experimenter pulled down a lever, a horizontal bar riding at both ends on parallel tracks squeezed the two bottles simultaneously (see Figure 1). This action expelled equal-sized aliquots of headspace into the subject's nostrils via a short length of Teflon-glass tubing that terminated in a conical nosepiece that fitted snugly into the nostril. The output of the squeezer (±SD) was 54.3 ml ± 1.2 ml. As the experimenter pulled down the lever, he instructed the subject to inhale through the nose. The subject's face was held in place by a forehead- and a chin-rest (see Figure 1).

Insert Figure 1 about here

Procedure.

Odor, nasal pungency, and eye irritation thresholds. These thresholds were measured using a two-alternative, forced-choice procedure with an ascending-concentration method of limits, as described earlier (Cometto-Muñiz and Cain 1995b). Briefly, the method required the participant to choose the stronger (odor, nasal pungency, or eye irritation) of two stimuli. One stimulus was a blank, i.e., diluent, the other a certain dilution step in a series. Testing began with the highest dilution step (i.e., the lowest concentration) and progressed to stronger levels whenever the subject chose incorrectly. The first step chosen correctly five times in a row was taken as the threshold. To avoid depletion of headspace no bottle ever succeeded itself, but rather was succeeded by a duplicate; at least 45 sec elapsed between pairs of bottles; and the bottles were shaken in a circular pattern before presentation. The interstimulus interval of 45 sec and the use of an ascending series of presentations served to minimize olfactory adaptation (Cometto-Muñiz and Cain 1995a).

In previous studies of odor and nasal pungency thresholds, participants squeezed the bottles themselves by hand. In the present investigation nasal localization thresholds needed to be measured by mechanical squeezing. For comparability, we measured odor and nasal pungency thresholds in this study with both procedures: hand-squeezing by the subjects, and mechanical squeezing by the experimenter.

Nasal localization thresholds. The two-alternative forced-choice procedure with presentation of progressively higher concentrations was also employed to measure thresholds for nasal localization in normosmics and anosmics. The mechanical squeezer presented matched volumes of headspace from two bottles that led, respectively, to the right and left nostrils. One bottle contained the stimulus and the other a blank. A trial consisted of two successive presentations of two bottles. On one presentation, the bottle that contained the stimulus fed vapor into the right (left) nostril, and on the next presentation the bottle that contained stimulus fed vapor into the left (right) nostril.

When the experimenter was testing localization in the right nostril, he asked the subject which presentation led to a stronger perception in the right nostril. When the experimenter was testing localization in the left nostril, he asked the subject which presentation led to a stronger perception in the left nostril. Incorrect choices led to presentation of the next stronger stimulus and correct choices led to presentation of the same step. The interstimulus interval was at least 45 sec. Five correct choices in a row for a given nostril was the criterion for the localization threshold.

The order of presentation of the five chemicals, the order of testing of the various types of thresholds, and the order for testing right or left nostril/eye varied irregularly from subject to subject. Every subject provided for each nostril/eye four measurements of each of the four types of thresholds: 1) odor (normosmics) or nasal pungency (anosmics) by hand–squeezing, 2) the same by mechanical squeezing, 3) nasal localization, and 4) eye irritation.

Data analysis. The geometric mean summarized the results across repetitive measurements for the same individual and across individuals since sensory thresholds tend to show a log normal distribution (Amoore 1986, Brown et al. 1968, Cain and Gent 1991). No systematic differences were observed across the two nostrils or eyes of the same subject.

Results

The first question explored was how odor and nasal pungency thresholds obtained by hand–squeezing the bottles compared with those obtained by mechanical squeezing. Figure 2 illustrates the outcome. Odor and nasal pungency thresholds obtained by hand–squeezing tended to lie slightly below those obtained by mechanical squeezing. Analysis of variance (ANOVA) on the odor thresholds (log ppm) revealed a

significant difference for the factor <u>alcohol</u> (i.e., chain–length) (p<0.002), but neither for the factor <u>technique</u> (i.e., hand–squeezing vs. mechanical squeezing) nor for the interaction <u>alcohol</u> X <u>technique</u>. An ANOVA on nasal pungency thresholds (log ppm) revealed a significant difference for the factor <u>alcohol</u> (p=0.0001), but neither for the factor <u>technique</u> nor for the interaction <u>alcohol</u> X <u>technique</u>. The interaction barely fell short of significance (p=0.051), reflecting a tendency for the difference between nasal pungency thresholds obtained with the two techniques to decrease as carbon chain–length increased (see Figure 2). 1–Octanol failed to evoke nasal pungency in the anosmics in either all instances (for 3 anosmics) or most instances (for 2 anosmics), so no value is plotted in Figure 2. In fact, some fragility in evocation of nasal pungency began with 1–hexanol, and the extent of it depended on the squeezing procedure employed: Via mechanical squeezing, three anosmics failed to reach a nasal pungency threshold for 1–hexanol in 3, 4, and 5 out of 8 instances, respectively. Via hand–squeezing, one anosmic failed to reach a pungency threshold in 1 out of 8 instances. Results plotted for 1–hexanol, then, reflect the average of those instances where a threshold was obtained.

Insert Figure 2 about here

The second question explored was nasal localization thresholds in normosmics and in anosmics. Figure 3 shows that average nasal localization thresholds of these alcohols in anosmics are higher than in normosmics by a factor of 1.27. The factor turned out nonsignificant: ANOVA on localization thresholds (log ppm) revealed a significant difference for the factor <u>alcohol</u> (i.e., chain–length) (p=0.0001), but neither for the factor <u>osmicity</u> (i.e., normosmics vs. anosmics) nor for the interaction <u>alcohol</u> X <u>osmicity</u>. It should be pointed out, however, that four of the five anosmics had one or another degree of difficulty in localizing 1–hexanol. For them, the number of instances in which a localization threshold could not be measured ranged between 2 and 6 out of 8

occasions. By contrast, each of the four normosmics localized 1-hexanol on all 8 occasions. Finally, neither the anosmics nor the normosmics could localize 1-octanol reliably. Hence, localization thresholds and nasal pungency thresholds described a similar picture of nasal trigeminal sensitivity, which extended to the absence of responses to 1-octanol (Figure 3).

Insert Figure 3 about here

A third question of interest concerned whether eye irritation thresholds in anosmics and normosmics would agree, and whether these would in turn agree with those for nasal pungency. Figure 4 shows that eye irritation thresholds for the two groups tended to agree. ANOVA on eye irritation thresholds (log ppm) revealed a significant difference for the factor alcohol (i.e., chain-length) (p=0.0001), but neither for the factor osmicity (i.e., normosmics vs. anosmics) nor for the interaction alcohol X osmicity. As observed before (Cometto-Muñiz and Cain 1995b), eye irritation and nasal pungency thresholds fell reasonably well into register (Figure 4), except for 1-octanol, the compound with an indeterminate nasal pungency threshold and localization threshold. Regarding earlier measurements of the threshold for nasal pungency of 1-octanol (Cometto-Muñiz and Cain 1990), one of three anosmics had failed to detect it most of the time, and, as a group, the anosmics had failed to detect it in 25% of instances.

Insert Figure 4 about here

Discussion

Nasal localization thresholds in normosmics appear to be approximately equivalent to nasal pungency thresholds in anosmics as indices of nasal chemesthetic

sensitivity. Before a broad generalization can be made, however, the degree of equivalence should be confirmed by testing additional VOCs and subjects.

Eye irritation thresholds, which reflect chemesthetic sensitivity in another mucosa, did not differ significantly between normosmics and anosmics of similar age, gender and smoking status. The present results reproduce, within a single study and within subjects, a previous finding of general agreement between nasal pungency and eye irritation thresholds for relatively nonreactive VOCs (Cometto–Muñiz and Cain 1995b). This conclusion holds for stimulation over the first few seconds. Over time of exposure, eye irritation may grow to surpass nasal irritation (Cain et al. 1987).

When nasal pungency thresholds, unbiased by odor sensations, began to be gathered via testing anosmics, it was noticed that normosmics often reported considerable pungency at, or even below, the anosmics' thresholds (Cometto–Muñiz and Cain 1990). A later study found a similar result (Kendal–Reed and Walker 1996). This could have reflected confusion between pungency and strong odor sensations in normosmics, or it could have reflected different sensitivity to pungency between anosmics and normosmics. A recent investigation on chemo–somatosensory event–related potentials using carbon dioxide (CO_2) as stimulus found normosmics to produce a marginally larger peak–to–peak amplitude in the early P1N1 wave than did persons with olfactory impairment, either hyposmia or anosmia (Hummel et al. 1996). This outcome may have relevance to whether anosmics have lower sensitivity to pungency than do normosmics, as discussed below. The mechanism for any such difference remains strictly a matter of speculation.

The present results did not demonstrate the significantly lower nasal localization thresholds in normosmics that would be expected if intact olfaction facilitated

chemesthetic activation. On strict statistical grounds, the outcome suggested that nasal detection thresholds in anosmics or nasal localization thresholds (in either group) do indeed reflect the concentration at which a compound begins to evoke true pungency in persons with a normal sense of smell. Nevertheless, on average normosmics did yield lower chemesthetic thresholds, particularly for nasal localization. A larger group of subjects will be needed to establish the generality of this finding. The question of whether normosmics can detect pungency at lower levels than anosmics therefore remains open. The effect, if real, seems in any event small. We also note that a study of irritation–induced reflex changes in respiration in mice implid no effect of anosmia on sensitivity to nasal irritation (Hansen et al. 1994).

Our <u>odor thresholds</u>, obtained with uniform methodology, have correlated well (r=0.83, n=35) with those compiled, standardized and averaged by Devos et al. from the literature (Devos et al. 1990). Nevertheless, about three quarters of our thresholds lie above those of Devos et al. Higher thresholds could stem from: 1) a requirement for perfect detection to reach criterion rather than the more customary 50% detection above chance, and 2) monorhinic testing per se, and therefore an absence of bilateral summation across the nostrils (see Cain 1977). Such factors would presumably affect odorants equally which should leave <u>relative</u> potency unaltered. Comparative sensory potency, measured with convenient methodology, has been the main focus of the research. Odor thresholds have consistently showed more variability than nasal pungency thresholds (Cometto–Muñiz and Cain 1994a).

Our <u>nasal pungency thresholds</u> — measured in anosmics — tend to be higher than those reported in the only relatively recent review of human irritation thresholds (Ruth 1986). On average, across 16 compounds common to the two sources, our thresholds lie above those in the review by about an order of magnitude. However, the

compiled thresholds were measured in participants with normal olfaction and are, therefore, subject to confounding by odor.

It has been pointed out that sensory irritation serves as the effect responsible for Threshold Limit Values (TLVs) in almost half the cases (Alarie 1981). The RD_{50} obtained in the assays of irritation in mice showed a high correlation with existing TLVs (Alarie 1981). For the nonreactive substances studied both by the respiratory depression technique and by human psychophysical judgment, the correlation is also high (Cain and Cometto–Muñiz 1995, Cometto–Muñiz and Cain 1994b). The use of human odor and nasal pungency thresholds in practical applications, such as to set TLVs based on sensory irritation, can be hampered by at least three considerations: the methodology used to obtain the thresholds, the exposure time, and possible sensory interactions in mixtures of chemicals.

Our thresholds represent acute sensory reactions to short–term stimuli (1–2 sec). They do not reflect effects over time. Typically, odor sensations fade with time continuously over some minutes. This process of olfactory adaptation shifts odor thresholds up (for a review see Cometto–Muñiz and Cain 1995a). In contrast, pungent or irritant sensations tend to increase in magnitude during many minutes with continuous stimulation, which suggests that thresholds could be shifting down. What most studies have shown under environmentally realistic exposures (e.g., Cain et al. 1986, Hudnell et al. 1992, Otto et al. 1990) is that ratings of perceived sensory irritation may increase with time, particularly in early stages of exposure, but the studies have not looked at direct measures of sensitivity, e.g., irritation thresholds, to confirm that such thresholds have concomitantly decreased.

One ultimate goal is to provide environmentally realistic sensory thresholds, such as those encountered in whole–body exposures. These values are needed, for example, to set threshold limit values based on a sensory endpoint. It needs to be established if thresholds obtained with the simple "squeeze bottle technique" can be readily converted, through the use of a uniform factor for all nonreactive chemicals, to environmentally relevant values or if the conversion factor varies for different groups of chemicals. Research in this laboratory is at present addressing the issue.

Acknowledgments

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Figure Legends

Figure 1. Experimental set–up showing the experimenter activating the mechanical squeezer and the subject leaning on a head– and chin–rest, with nosepieces in place.

Figure 2. Nasal pungency and odor thresholds, obtained by hand–squeezing and by mechanical squeezing, as a function of carbon chain–length of the homologous n–alcohols. Bars indicate standard deviations (SD).

Figure 3. Nasal localization thresholds in anosmics and normosmics as a function of carbon chain–length of the n–alcohols. Nasal pungency thresholds by mechanical squeezing (in anosmics) are shown for comparison. Bars indicate standard deviations (SD).

Figure 4. Eye irritation thresholds in anosmics and normosmics as a function of carbon chain–length for the n–alcohols. Nasal pungency thresholds by hand–squeezing (in anosmics) are shown for comparison. Bars indicate standard deviations (SD).
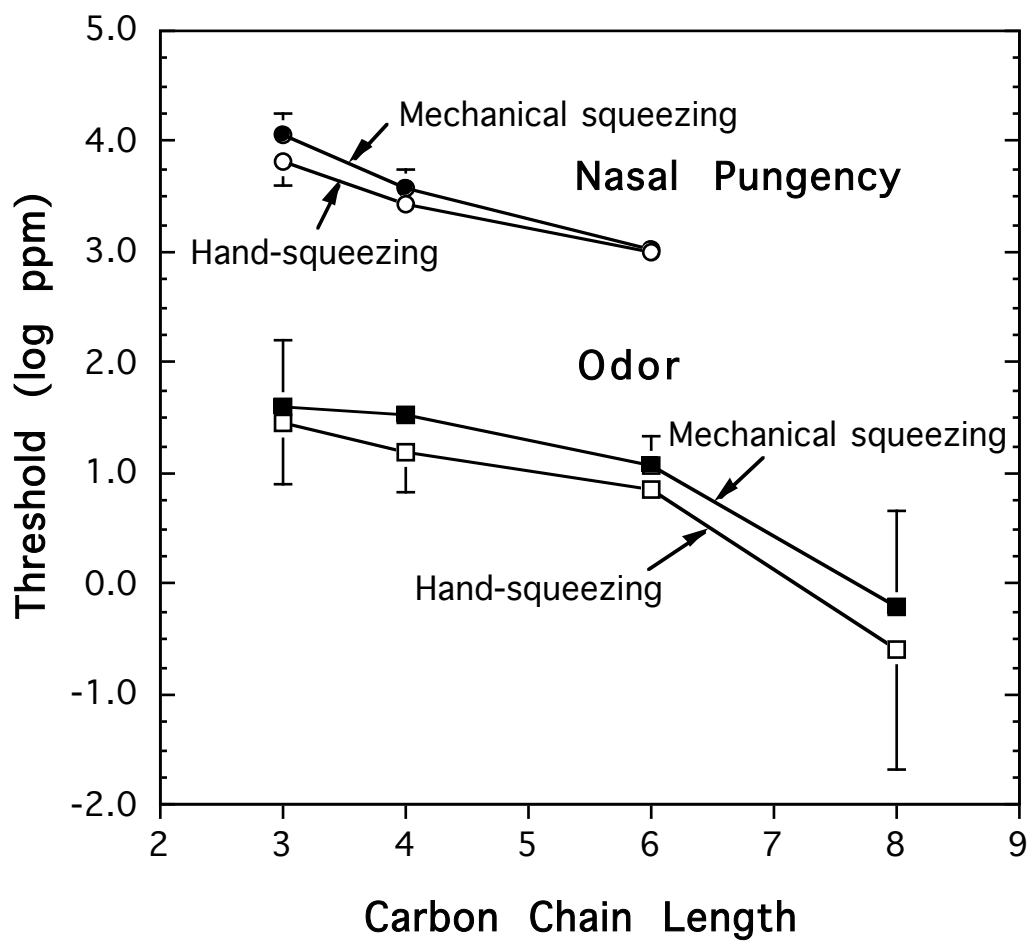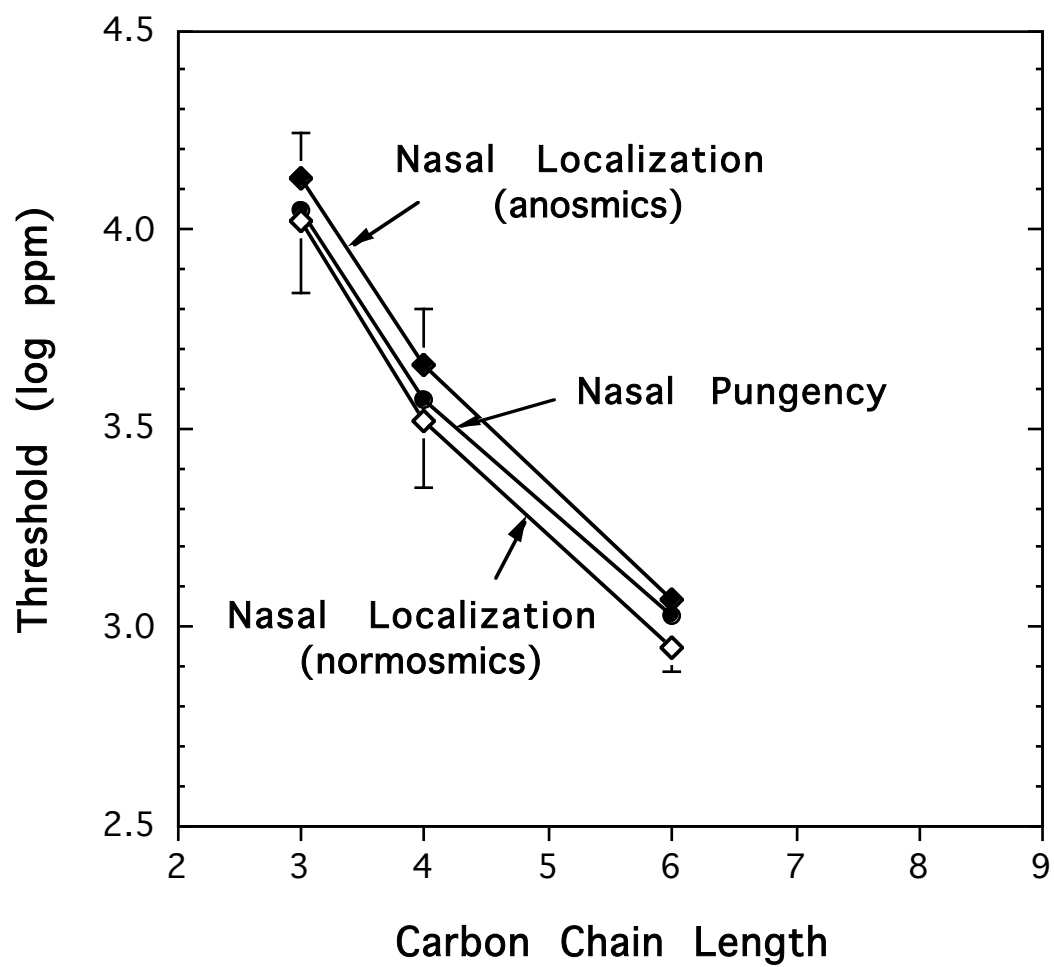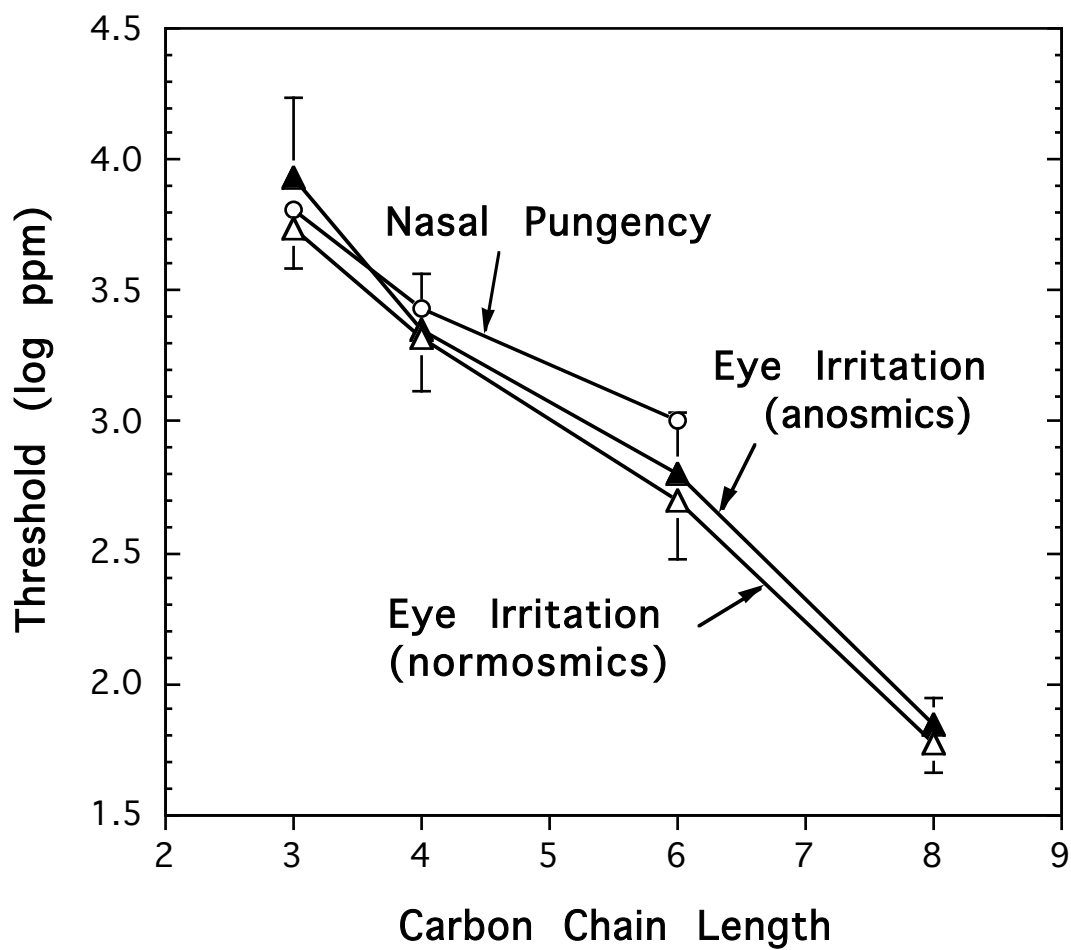
FIGURE 1 (NOT INCLUDED)

FIGURE 2

FIGURE 3

FIGURE 4