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Nasal chemosensory irritation in humans

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Introduction

The detection of external chemicals by humans is accomplished by smell (olfaction), taste (gustation), and chemical sensory irritation (1-4). The latter was originally labeled the common chemical sense (5). More recently it has been referred to as chemical nociception (6). Nevertheless, at low levels of stimulation, the sensations evoked might not be perceived as painful or even irritating. Since this sensory modality rests on chemically-induced somesthesis, or chemical "feel", the quite appropriate and descriptive term "chemesthesis" is now often employed (3, 7, 8). In the nasal, ocular, and oral mucosae, chemesthesis is principally mediated by the trigeminal nerve (cranial nerve V). Thus, it is common to refer to trigeminal chemosensitivity when addressing this topic (9, 10). In the aggregate, eye, nose and throat irritation have been referred to as "sensory irritation," and along with secondary reflex symptoms in that anatomical distribution, constitute an important symptom constellation in so-called "problem buildings," as well as being the basis for a substantial fraction of occupational exposure standards (11, 12). Nasal chemesthesis, the main focus of this chapter, arises from stimulation with airborne chemicals. Many of these, although not all of them, are volatile organic compounds (VOCs). The chemesthetic sensations that they can evoke in the nose are typically pungent, i.e., sharp. They include: stinging, freshness, coolness, burning, piquancy, tingling, irritation, prickling, and the like.

Most, if not all, volatile compounds capable of eliciting nasal chemesthesis also elicit olfactory sensations. With few exceptions (e.g., ß-phenyl ethyl alcohol), compounds that smell, i.e., odorants, can also evoke nasal chemesthesis. As a rule, when the concentration of an

airborne chemical rises, it is first noticed by its smell, but as it continues to rise it also engages a chemesthetic response. It is then important to define the concentration range at which a substance remains undetected, that at which it evokes only an olfactory response, and that at which it evokes an olfactory plus a trigeminal response (13). Carbon dioxide (CO_2) is a compound that, arguably, only elicits chemesthesis with little, if any, smell. On the other hand, some compounds do have a smell but fail to evoke chemesthesis. Such chemicals have been often found by testing homologous series of VOCs, where a certain homolog is reached beyond which chemesthesis cannot be elicited (14) (see the "cut-off" effect section below).

In view of the higher olfactory than trigeminal sensitivity, and the scarcity of compounds that evoke nasal chemesthesis but not smell, it was a challenge to implement bias-controlled (e.g., forced-choice) psychophysical procedures to gauge nasal chemesthesis independently of olfaction. One strategy to achieve this goal entailed testing nasal detection of chemical vapors in subjects lacking a functional olfaction (i.e., anosmics) and, thus, only responding to trigeminal chemesthesis. Another strategy, entailed employing subjects with normal olfaction (i.e., normosmics) in a task requiring not the detection but the localization (lateralization) of the vapor to the left or right nostril when air is simultaneously delivered to the contralateral nostril (15-17). Nasal localization rests on trigeminal input (18, 19) rather than on olfactory input as originally thought (20). The following sections describe these and other strategies to study nasal chemesthesis in humans.

Psychophysics of Nasal Irritation

Nasal pungency thresholds (NPTs) in anosmics

As mentioned, testing anosmic subjects in tasks of nasal detection of vapors represents one way to eliminate the biasing influence of olfaction in estimating the nasal chemesthetic potency of airborne chemicals (21, 22). These early papers suggested that relatively simple physicochemical and molecular structural properties could predict nasal chemesthesis. Nevertheless, the lack of a guiding unit of chemical change among the very wide range of compounds capable of evoking nasal irritation, made it difficult to pursue a systematic study of chemesthetic potency across VOCs, for example, by measuring nasal pungency thresholds (NPTs). Along homologous chemical series, carbon chain length constitutes a practical unit of chemical change. This strategy was applied in a series of studies that measured NPTs in anosmics and odor detection thresholds (ODTs) in normosmics for homologous alcohols, acetate esters, 2-ketones, n-alkylbenzenes, aliphatic aldehydes, and carboxylic acids, and for selected terpenes, using a uniform methodology (23-28). The method comprised a two-alternative forced-choice procedure, an ascending concentration approach, and a fixed criterion of five correct choices in a row. The outcome showed that both NPTs and ODTs decline with carbon chain length along n-homologs in each series (Figure 1). Lower thresholds indicate higher potency of the stimulus. NPTs lay between one and five orders of magnitude above ODTs. The simple delivery system (i.e., “squeeze bottles”) used to obtained these thresholds, combined with the stringent criterion chosen to define them, had produced values on the higher end of reported thresholds. Indeed, improved techniques and methodologies did render lower absolute thresholds but left the relative chemesthetic and olfactory potency across VOCs virtually unaltered (29-31). Interestingly, in terms of nasal pungency, many of these series reached a large enough homolog

that failed to be detected consistently by one or more anosmics, even at vapor saturation (27). Once such homolog was reached, the failure to detect (i.e., to elicit nasal pungency) became increasingly more evident for all ensuing homologs. In other words, the increasing nasal pungency potency of successive homologs (reflected in decreasing thresholds) ended rather abruptly upon reaching a member that lacked potency altogether. This cut-off effect in chemesthesis is discussed below.

Insert Figure 1 about here

The use of anosmics to gauge nasal trigeminal sensitivity presumes that the lack of olfaction in these subjects does not alter to a significant extent chemesthetic sensitivity, compared to normosmics. A number of investigations have explored this issue but the results have been mixed. In behavioral tests where anosmics showed lower sensitivity and intensity ratings for chemesthesis, normosmics were not "blind" to the odor of the stimuli, which could have affected the results (32, 33). Congenital anosmics tested with CO_2 gave lower intensity ratings than normosmics (34), but anosmics after upper respiratory tract infection (URI) and those after head trauma gave intensity ratings no different than those from normosmics (35). Still, anosmics after URI and those after head trauma, but not hyposmics, had higher CO_2 detection thresholds than normosmics (36). Unfortunately, these CO_2 thresholds were obtained from yes-no answers (quite prone to criterion-based biases) rather than from a more robust forced-choice procedure. Electrophysiological tests on nasal chemesthesis have included peripheral responses, namely the negative mucosal potential (NMP), and central responses, namely trigeminal event related potentials (tERP) generated in the cortex. For peripheral

responses to CO_2 stimulation, congenital anosmics and those from acquired etiologies had a larger activation than normosmics (34, 35). In contrast, for central responses to CO_2 stimulation, congenital anosmics showed no significant differences with normosmics (34), whereas anosmics from acquired etiologies (and hyposmics) had a significantly smaller activation than normosmics. The specific component(s) responsible for this smaller central activation remain unclear since in some instances the smaller activation has occurred for the peak-to-peak amplitude of the early P1N1 wave (37), and, in other instances, for the base-to-peak amplitude P2 and peak-to-peak amplitude N1P2 (35).

Nasal localization thresholds (NLTs)

The nasal lateralization task provided a good opportunity to compare the chemesthetic performance of normosmics and anosmics. Again, the results were mixed. Congenital anosmics did not differ from normosmics in their ability to lateralize neat eucalyptol (34). In contrast, hyposmics and anosmics from acquired etiologies did poorer than normosmics in their ability to lateralize neat benzaldehyde and eucalyptol, with the difference sometimes reaching statistical significance (38) and sometimes not (35).

Subjects with normal and absent olfaction were tested for NLTs under an ascending concentration approach that included dilutions of the chemicals, not only the neat compound, and that involved quantification of vapors by gas chromatography. Homologous n-alcohols, selected terpenes, and cumene served as stimuli (16, 28). The outcome showed a picture of slightly higher sensitivity (lower NLTs) for normosmics compared to anosmics, but the difference did not

achieve statistical significance (Figure 2). Overall, the three estimates of nasal chemesthesis (NLTs in normosmics, NLTs in anosmics, and NPTs) and even ocular chemesthesis (i.e., eye irritation thresholds, EITs) often provided a similar picture of trigeminal sensitivity for each VOC (Figure 2). We note that some compounds could not reach the specific criterion for nasal and/or ocular threshold in all participants on all repetitions (even when presented neat), see details in (16, 28). Among the n-alcohols, 1-octanol did not achieve the NLT criterion in either normosmics or anosmics, and very often failed to achieve it for NPTs; nevertheless, octanol did reach EIT in both groups (16) (Figure 2). Among the terpenes, delta-3-carene and 1,8-cineole were the most reliable chemesthetic stimuli, reaching NPT, NLT and EIT (the last two in normosmics and anosmics) in virtually all subjects and repetitions, whereas geraniol very commonly failed to reach criterion for these same thresholds (28) (Figure 2). Based on the results presented in this and the previous section we conclude that any advantage in nasal chemesthetic sensitivity that normosmics might have over anosmics, if indeed real, appears relatively small.

Insert Figure 2 about here

Cut-off point for eliciting chemesthesis along vapors from homologous series

As noted above, thresholds for nasal (and ocular) chemesthesis decline with carbon chain length along homologous series, but only until reaching a large enough homolog that begins to fail to evoke chemesthetic detection altogether, even at vapor saturation at room temperature (≈23°C). The point where this happens within each series has been labeled the cut-off point for chemesthesis, and the shortest homolog failing detection, the cut-off homolog (13). A number of

recent studies, particularly in the ocular mucosa, have defined the cut-off homolog for various series, and have provided indications on the likely basis for the effect in terms of a structure-activity context (14, 39-45). This is discussed next.

The appearance of a cut-off effect in the detection of chemesthesis from homologous vapors can rest on at least two possibilities. One is that the series has reached a member whose vapor pressure is too low to reach the necessary threshold concentration. Another is that the series has reached a member who lacks a key property to trigger transduction. For example, the homolog might be too large to interact effectively with a target site or a binding pocket in a receptive macromolecule. To look into these issues we devised three approaches. The first approach consisted in applying a successful quantitative structure-activity relationship (QSAR), based on a solvation equation (46), to calculate and model predicted NPTs along homologous series (47-49). (This QSAR for nasal chemesthesis is described in detail in Chapter 25, "Physico-chemical modeling of sensory irritation in humans and experimental animals".) Then, trends in measured and calculated NPTs were compared with trends in saturated vapor concentrations at room temperature (23°C) and at body temperature (37°C) across homologs. The outcome showed that an extrapolation of the trend depicted by measured and calculated NPTs to the point of the cut-off homolog produced a predicted NPT concentration lower than the saturated vapor at 23°C (acetates case) or lower than that at 37°C (alcohols case) (Figure 3). We conclude that: a) for the acetates, the cut-off was not likely the result of a low vapor concentration, and b) for the alcohols, if indeed the cut-off resulted from a low vapor concentration, raising the concentration of the cut-off homolog to vapor saturation at 37°C should overcome the effect and precipitate detection. The outcome of this strategy is discussed next.

Insert Figure 3 about here

The second approach consisted in testing the chemesthetic detection of each cut-off homolog at vapor saturation at 37°C, where the concentration for both compounds (decyl acetate and 1-undecanol) will be clearly above the predicted threshold (see Figure 3). For decyl acetate, the test has been performed for both nasal and ocular chemesthesis. The results for nasal chemesthesis revealed no significant increase in its detection at the higher vapor saturation, arguing against a cut-off based on a concentration restriction (14) (Figure 4). The results for ocular chemesthesis did find a slight, but significant, increase, for the group data; but analysis of the individual data revealed that the increase was only seen for half of the 12 participants, whereas the other half did not show it at all (39). It was suggested that the exact cut-off point might vary slightly among subjects, perhaps due to genetic variability in the receptors involved. For 1-undecanol, the test involving increased vapor saturation has been, so far, only performed for ocular chemesthesis. The results mimicked those obtained for decyl acetate in the eye, including the sharp contrast between the performance of two subgroups of subjects (39).

Insert Figure 4 about here

The third approach to probe into the basis for the cut-off effect has been only explored in the ocular mucosa, up to the moment. It consists in measuring concentration-detection functions for chemesthesis, instead of only a threshold value, and establishing whether the function for the cut-off homolog reaches a plateau at some low level of detection such that further increases in

concentration fail to increase detectability. The results from studies of homologous alcohols, acetates, alkylbenzenes and 2-ketones have supported the existence of this kind of plateau for the respective cut-off homolog: 1-undecanol, decyl acetate, heptylbenzene, and 2-tridecanone (44, 45). The outcome provides additional support to the idea that the cut-off often emerges from a restriction other than vapor concentration; for example, it could emerge from the homolog exceeding a critical molecular dimension to activate chemesthesis.

Nasal chemesthesis and exposure time

Nasal irritation from chemicals often increases with time of exposure until reaching a plateau and, sometimes, declining thereafter (50). At the perithreshold level and for short exposures (<10 sec), this temporal effect produces lower chemesthetic thresholds as stimulus duration increases. Whether measured with a trigeminally-induced reflex apnea (51) or with the nasal lateralization technique, temporal integration of threshold nasal chemesthesis has been described for ammonia, CO_2, and the n-alcohols ethanol, butanol, and octanol (52-56). The outcome suggests that, within a short time-frame (≈4 sec) detection of nasal chemesthesis relies on total mass rather than on concentration of the stimulus. However, the relationship between time and concentration falls, to a smaller or larger degree, short of a perfect trading: It takes somewhat more than doubling the exposure duration to compensate for a twofold decrease in concentration.

Suprathreshold ratings of nasal chemesthesis (i.e., perceived intensity) increase with stimulus duration, at least for up to about 4 sec, as shown for ammonia (53, 56) and CO_2 (57). In

addition, the amplitude of the P3 peak from the tERP response to CO_2 also increases with stimulus duration in the very-short range of 100 to 300 msec (58). Chamber studies with formaldehyde at a fixed concentration showed that the perceived intensity of (nasal and ocular) chemesthesis grows steadily with time during the 29-min exposure (59). Daily home or occupational exposure to an airborne chemical that might be causing mild irritation can increase the nasal chemesthetic threshold to that chemical (i.e., produce desensitization) but the effect does not seem to generalize to other irritants (15, 60, 61). Experiments entailing 2 to 3 hours exposures to mixtures of VOCs (62) and to environmental tobacco smoke (63) showed that the perceived intensity of chemesthesis clearly increases with time.

Nasal chemesthesis and chemical mixtures

Most, if not all, the studies we have discussed have dealt with the production of chemesthesis in humans from exposures to single chemicals. In contrast, environmental exposures at work and at home, indoors and outdoors, typically involve the presence of complex mixtures of compounds (64). It is, then, very relevant to explore and understand how the human nasal chemesthetic system processes mixtures of irritants. For convenience, we can distinguish those investigations that focused on the perithreshold level, i.e., detection of nasal irritation by mixtures, from those that focused on the suprathreshold level, i.e., magnitude (or intensity) of nasal irritation by mixtures. Under both strategies, one important goal is to uncover the rules that govern the chemesthetic impact of the mixture as compared to that of the individual components.

Human investigations addressing the nasal chemesthetic intensity of chemical mixtures are relatively few compared to those in olfaction. The total nasal perceived intensity of mixtures of the pungent odorants ammonia and formaldehyde grew with concentration in a way indicating that the perception of the mixture switched from being significantly lower to being significantly higher than the sum of the perceived intensities of its components (65). This suggested that an increase of the relative contribution of nasal chemesthesis over olfaction underlay the effect, an interpretation later confirmed in additional experiments (66). The complex stimuli environmental tobacco smoke elicited both nasal and ocular chemesthesis, although the ocular mucosa seemed the most sensitive (63). These studies have relied on instructing the subjects to assess separately the odorous and the chemesthetic (pungent) component of the nasal sensation, a task quite prone to different biases across subjects (67, 68).

Regarding the perithreshold detection of mixtures, an intensive study of 9 single chemicals and their mixtures, including two three-component, two six-component, and one nine-component mixtures, observed various degree of agonism (additive effects) among the constituents (69). The outcome comprised not only NPTs, but EITs and ODTs as well. The use of short-chain and longer-chain homologs from four different series facilitated the interpretation of the results in physicochemical terms. The degree of chemosensory agonism became larger as the number of components and their lipophilicity increased. The chemesthetic thresholds showed stronger agonism than the olfactory ones, with eye irritation having stronger agonism than nasal pungency. While physicochemical properties were shown to play an important role in the chemosensory detection of single chemicals (see Figure 1), they seem to have relevance for

mixtures too. Later studies took a more comprehensive look at the study of mixtures by measuring not just threshold values but complete concentration-detection, i.e., psychometric or detectability, functions, see (30). This quite intensive and detailed approach geared the effort to the simpler case of binary mixtures. Again, components of the mixtures were selected form homologous series and included 1-butanol and 2-heptanone (70), butyl acetate and toluene (71), and ethyl propanoate and ethyl heptanoate (72). The idea behind this selection was to explore a pair from different series but with similar chemical functionality, a pair from different series with dissimilar functionality, and a pair from the same series and functionality. The results were analyzed in terms of response-addition (sum of detectabilities) and of dose-addition (sum of doses within a selected psychometric function). The overall results indicated relative agreement between response- and dose-addition, and, irrespective of the structural or chemical similarity between components, a stronger degree of addition of detection at low than at high levels of detectability (73). (We clarify that in these studies low levels of detectability were still above chance detection, and high levels were still below perfect detection.) Interestingly, nasal pungency showed a stronger degree of addition than eye irritation, particularly at high levels of detectability.

Complex mixtures of airborne compounds, e.g. environmental tobacco smoke (74), fragranced household products (75), indoor air (62, 76-78), and outdoor air surrounding composting facilities (79) or animal production facilities (80, 81), have been employed to assess their potential to elicit human mucosal sensory irritation. In these cases the focus has been exclusively on the total effect of the mixture, at one or another dilution level, on a healthy sample of subjects, or on two or more groups of subjects with or without a certain condition (for

example, asthmatics). No attempts were made to relate the chemesthetic impact of the mixture to that of the individual components. In fact, in some cases, the very complex mixtures could not be fully defined from a chemical standpoint.

Respiratory Behavior and Nasal Irritation

Reflex nasal transitory apnea

When a chemical irritant entering the nose reaches a certain level, a momentary and reflex interruption of breathing (apnea) occurs. This physiological effect has been employed to understand functional features of nasal chemesthesis and to assess the comparative chemesthetic sensitivity of groups of subjects by gender, age, and smoking-status (51, 56, 82-85). The results indicated that females, young individuals, and non-smokers are more sensitive than males, older individuals, and smokers, respectively, as probed by the reflex transitory apnea. The differences have been confirmed by psychophysical procedures (38, 82, 86-91). In addition, physiological techniques (e.g., rhinomanometry, NMP, tERP) have also been employed to study these and other group differences, for example, those due to nasal disease or condition, see reviews in (90, 92). These methods and outcomes are described in detail in Chapter 8, “Exposure and recording systems in human studies”.

Other respiratory behavior alterations

Airborne chemicals producing odor and irritation can change breathing parameters, for example, they can reduce tidal volume (93). The odorants acetic acid, amyl acetate, and phenyl ethyl alcohol were selected as representative of compounds possessing strong, medium, and null (or minimal) nasal trigeminal impact in an investigation that combined estimates of odor and nasal irritation with measurements of nasal patency and respiratory behavior (94). As expected, the compounds showed greater differences in nasal irritation than in odor strength. It was pointed out that tidal volume seemed to have a close and inverse relationship to nasal irritation.

Using a visual analogue scale, normosmics and anosmics estimated the magnitudes of odor and irritation evoked by the presentation of a wide range of concentrations of propionic acid, while their breathing characteristics were recorded (95, 96). As concentration increased, inhalation volume began to decline in normosmics at a lower concentration and at a faster rate than it did in anosmics. When normosmics first began to show this decline, their estimates of both odor and nasal irritation where already significantly higher than in the clean air condition (control). In contrast, inhalation duration began to decline at the same concentration in normosmics and anosmics, and it did it at a concentration where anosmics first reported nasal irritation. Still, as observed for inhalation volume, inhalation duration declined with concentration faster in normosmics than in anosmics. The authors favored the interpretation that the higher sensitivity of normosmics to a decline in inhalation volume validated their reports of nasal irritation at concentrations undetected by anosmics.

In an environmental chamber study, phlebotomists occupationally exposed to isopropanol and unexposed controls were challenged with a 400 ppm concentration of isopropanol (its time-

weighted average threshold limit value) during 4 hours (97). Exposures to phenyl ethyl alcohol and to clean air served as a negative control for irritation, and as a negative control for both odor and irritation, respectively. The only physiological end-point that changed exclusively in the isopropanol condition was respiratory frequency. It increased, relative to baseline, in both subject groups, with no differences among them. Since reports of irritation and odor intensity declined with time, the authors attributed the increase in respiration frequency to a voluntary change in breathing in response to an unpleasant, solvent-like odor (i.e., a cognitive mediation) rather than to a reflexive change due to sensory irritation (i.e., an autonomic event).

The significance of the phenomenon of irritant-induced respiratory alterations lies, at least in part, in establishing an analogy with (and basis for extrapolation from) animal studies of a similar endpoint. Several decades of work have documented the effects of irritants of different anatomical specificities (i.e., "sensory," "pulmonary," "respiratory") on breathing patterns in experimental animals. Alarie (98) coined the term "RD_{50}" to describe the endpoint of 50% reduction in respiratory rate that occurs upon exposure to (generally) water-soluble irritants with predominant impact on the upper respiratory tract (see Chapter 11, "Nasal reflexes – including alterations in respiratory behavior – in experimental animals."). Several reviews have since supported the relevance of the RD_{50} in predicting human sensory irritation (99-101) whereas other reviews remain skeptical of using the RD50 model for human risk assessment purposes (102, 103).

Summary

Nasal chemosensory irritation (i.e., chemesthesis) in humans results form stimulation of the trigeminal nerve. Almost all chemical vapors that produce odor can evoke nasal chemesthesis at higher concentrations, although there is a cut-off point along homologous series beyond which larger homologs fail to be detected by chemesthesis. The failure seems to rest on some aspect of molecular structure or dimensions rather than on a low vapor concentration. In turn, almost all irritants can also elicit an odor with the arguable exception of carbon dioxide (CO_2). To separate the trigeminal from the olfactory response of the nose, investigators have tested subjects lacking olfaction (i.e., anosmics) and have measured nasal lateralization thresholds, i.e., the ability to localize whether a vapor entered the right or the left nostril when air enters the contralateral nostril. Such ability rests on trigeminal, not olfactory input. Detection of nasal chemesthesis from chemical mixtures reveals additive effects among constituents, particularly at low levels of detectability (but still above chance detection). As a rule, increases in time of exposure decrease chemesthetic thresholds (i.e., enhances sensitivity) and produce higher ratings of irritation intensity. Nasal chemesthesis can produce alterations in respiration, including a reflex, transitory apnea, and reductions in the duration and volume of nasal inhalations. Relative consistency has been found for irritation thresholds among two of three anatomical structures subsumed within "sensory irritation" – i.e., the nose and eye. Thus for predictive toxicology and risk assessment purposes, an argument can be made that measurements using one system can often be extrapolated to the other.

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Figure Legends

Figure 1. Nasal pungency thresholds (NPTs) in anosmics and odor detection thresholds (ODTs) in normosmics for homologous alcohols, acetate esters, 2-ketones, n-alkylbenzenes, aliphatic aldehydes, and carboxylic acids, for cumene, and for selected terpenes. NPTs could not be measured for some compounds. Only n-homologs are joined by a line. Dashed lines indicate the appearance of a cut-off effect in NPTs such that one or more anosmics consistently failed to achieve the criterion chosen to reach an NPT. Bars indicate standard deviation (SD).

Figure 2. Showing nasal localization thresholds (NLTs) in normosmics and anosmics, and nasal pungency thresholds (NPTs) (by definition, always in anosmics) for homologous alcohols, selected terpenes, and cumene. For comparison, eye irritation thresholds (EITs) in normosmics and anosmics are also shown for the same VOCs. For some compounds, one or more types of thresholds could not be measured at all; for other compounds, some participants (normosmics and anosmics) could not achieve the criterion for chemesthetic threshold on all repetitions, see details in (16, 28). Bars indicate standard deviation (SD).

Figure 3. Above. Trends of measured and calculated NPTs, and of saturated vapor at 23 and 37 °C, as a function of the variable carbon chain length of n-acetates. The arrow points to the cut-off homolog (decyl acetate, C10) and shows that the saturated vapor concentration at 23°C is higher than the calculated (i.e., expected) threshold. Thus, the observed nasal pungency cut-off is unlikely to arise from a concentration restriction (14). Below. Analogous data for n-alcohols. The arrow points to the likely cut-off homolog (from experiments on ocular chemesthesis) (undecyl

alcohol, C11) and shows that, if the cut-off indeed arises from a low vapor concentration, raising the concentration to vapor saturation at 37°C should make undecyl alcohol detectable. This did not occur, at least for ocular chemesthesis (39).

Figure 4. Above. Homologs located at (decyl acetate) or beyond (octanoic acid) the cut-off point fail to increase their detection via nasal pungency (in anosmics) despite the increase in concentration achieved from vapor saturation at 23°C to vapor saturation at 37°C. In contrast, homologs located before the cut-off (octane) do increase their detection at the higher concentration. Below. The same homologs also fail to increase their detection when nasal chemesthesis is gauged via nasal localization (lateralization) in normosmics. In contrast, 2-undecanone, a homolog located just before the cut-off (which occurs with 2-tridecanone in the ketones series) does increase its detection. Bars indicate standard error (SE).

FIGURE 1

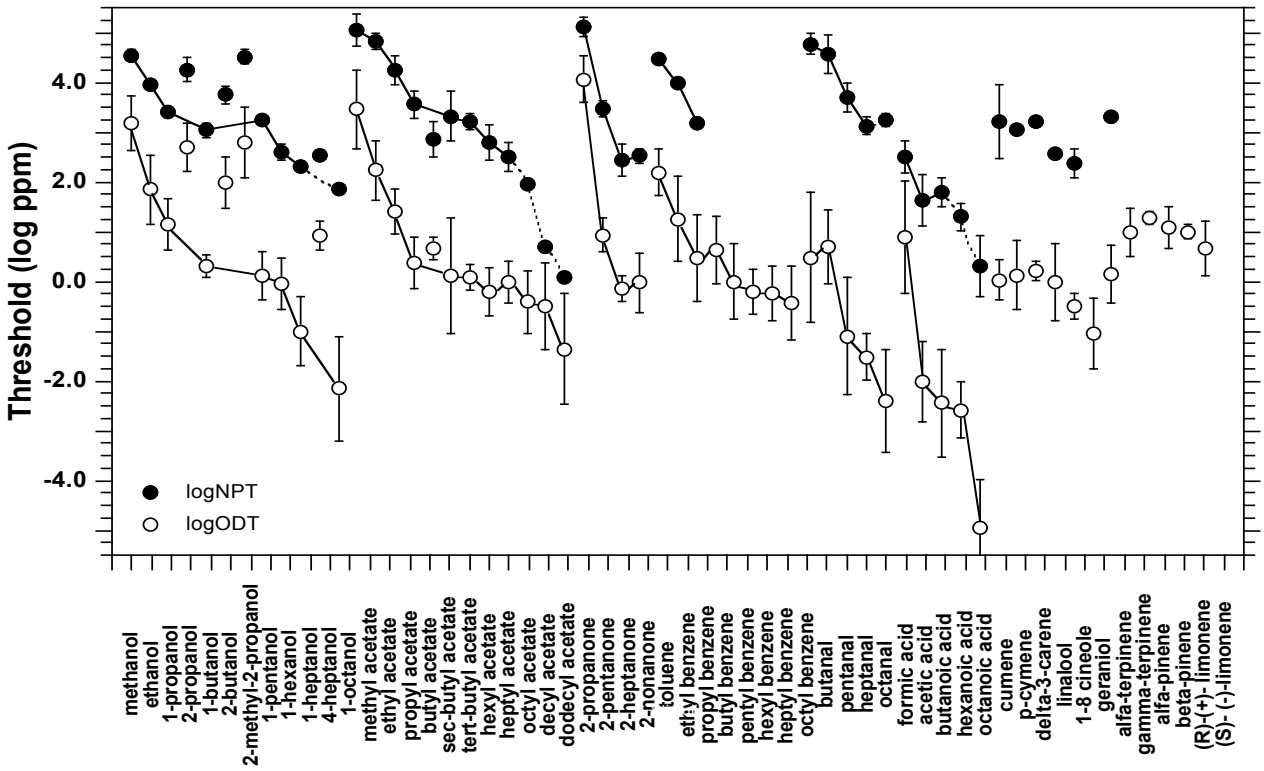

Threshold (log ppm)
4.0
2.0
0.0
-2.0
-4.0
logNPT
logODT
methanol
ethanol
1-propanol
2-propanol
1-butanol
2-butanol
2-methyl-2-propanol
1-pentanol
1-hexanol
1-heptanol
4-heptanol
1-octanol
methyl acetate
ethyl acetate
propyl acetate
butyl acetate
sec-butyl acetate
tert-butyl acetate
hexyl acetate
heptyl acetate
octyl acetate
decyl acetate
dodecyl acetate
2-propanone
2-pentanone
2-heptanone
2-nonanone
toluene
ethyl benzene
propyl benzene
butyl benzene
pentyl benzene
hexyl benzene
heptyl benzene
octyl benzene
butanal
pentanal
heptanal
octanal
formic acid
acetic acid
butanoic acid
hexanoic acid
octanoic acid
cumene
p-cymene
delta-3-carene
linalool
1-8 cineole
geraniol
alfa-terpinene
gamma-terpinene
alfa-pinene
beta-pinene
(R)-(+)- limonene
(S)- (-)-limonene

FIGURE 2

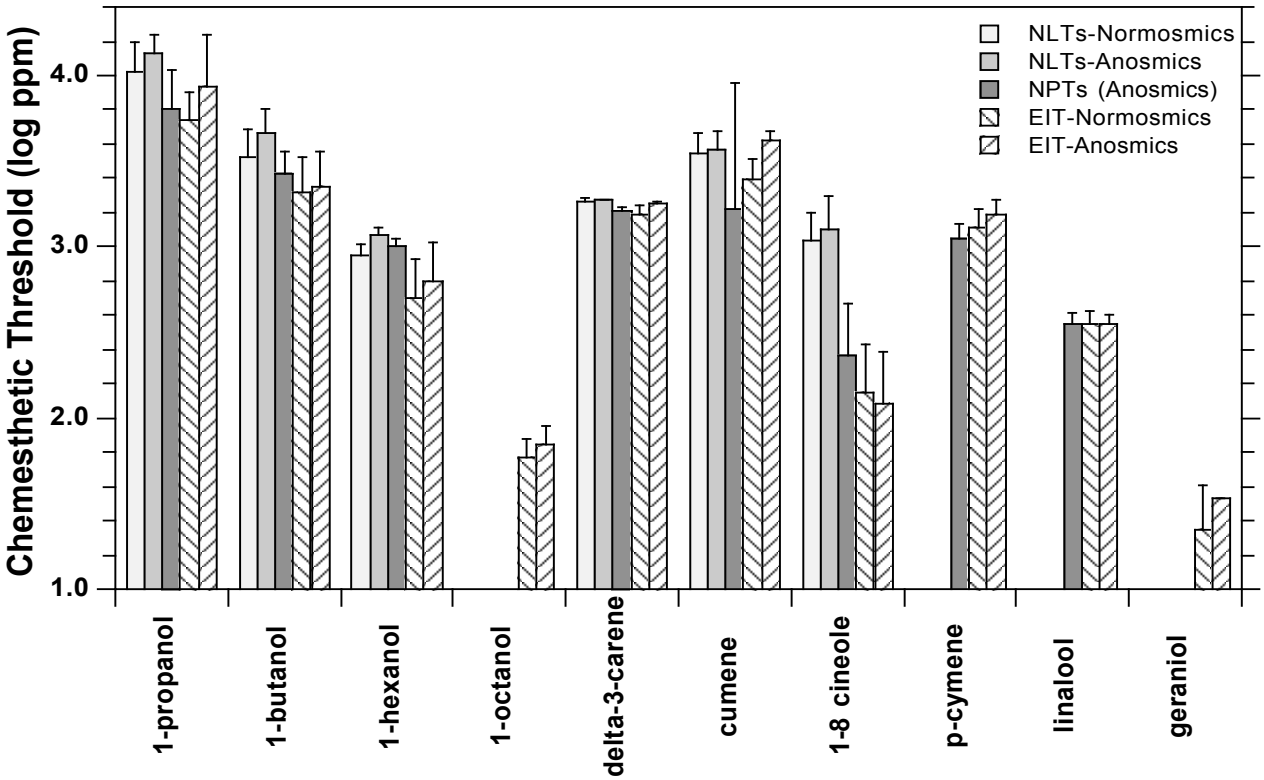
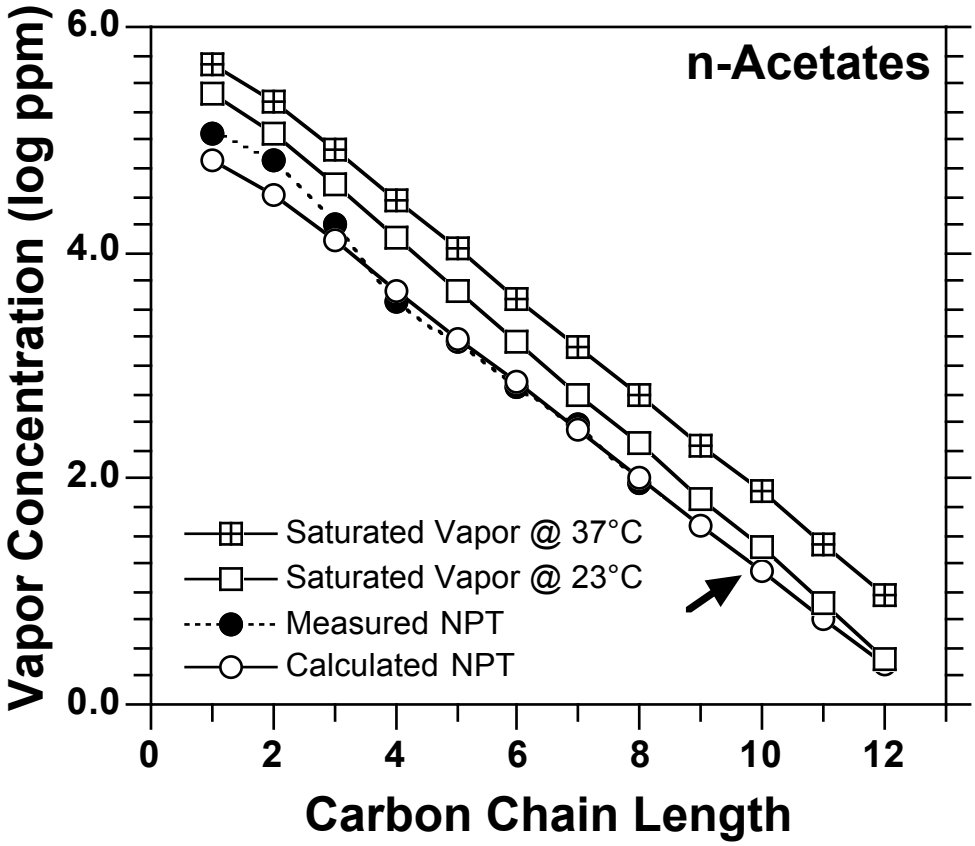

Chemesthetic Threshold (log ppm)
4.0
3.0
2.0
1.0
NLTs-Normosmics
NLTs-Anosmics
NPTs (Anosmics)
EIT-Normosmics
EIT-Anosmics
1-propanol
1-butanol
1-hexanol
1-octanol
delta-3-carene
cumene
1-8 cineole
p-cymene
linalool
geraniol

FIGURE 3


n-Acetates
Vapor Concentration (log ppm)
6.0
4.0
2.0
0.0
0
2
4
6
8
10
12
Carbon Chain Length
Saturated Vapor @ 37°C
Saturated Vapor @ 23°C
Measured NPT
Calculated NPT

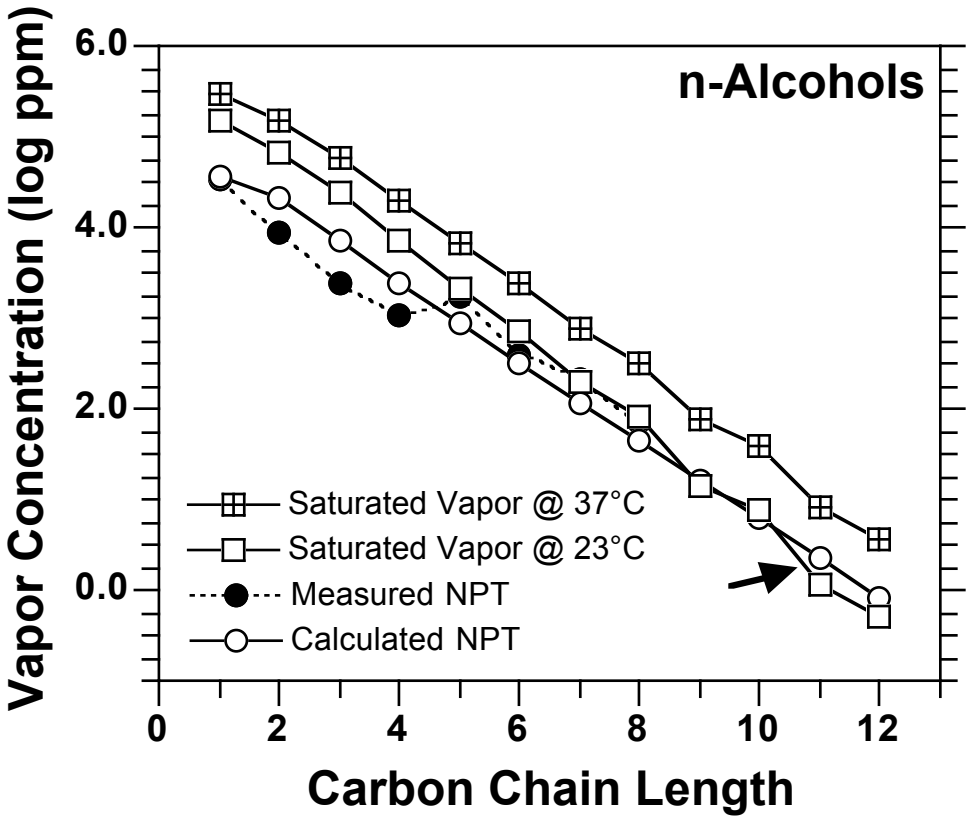
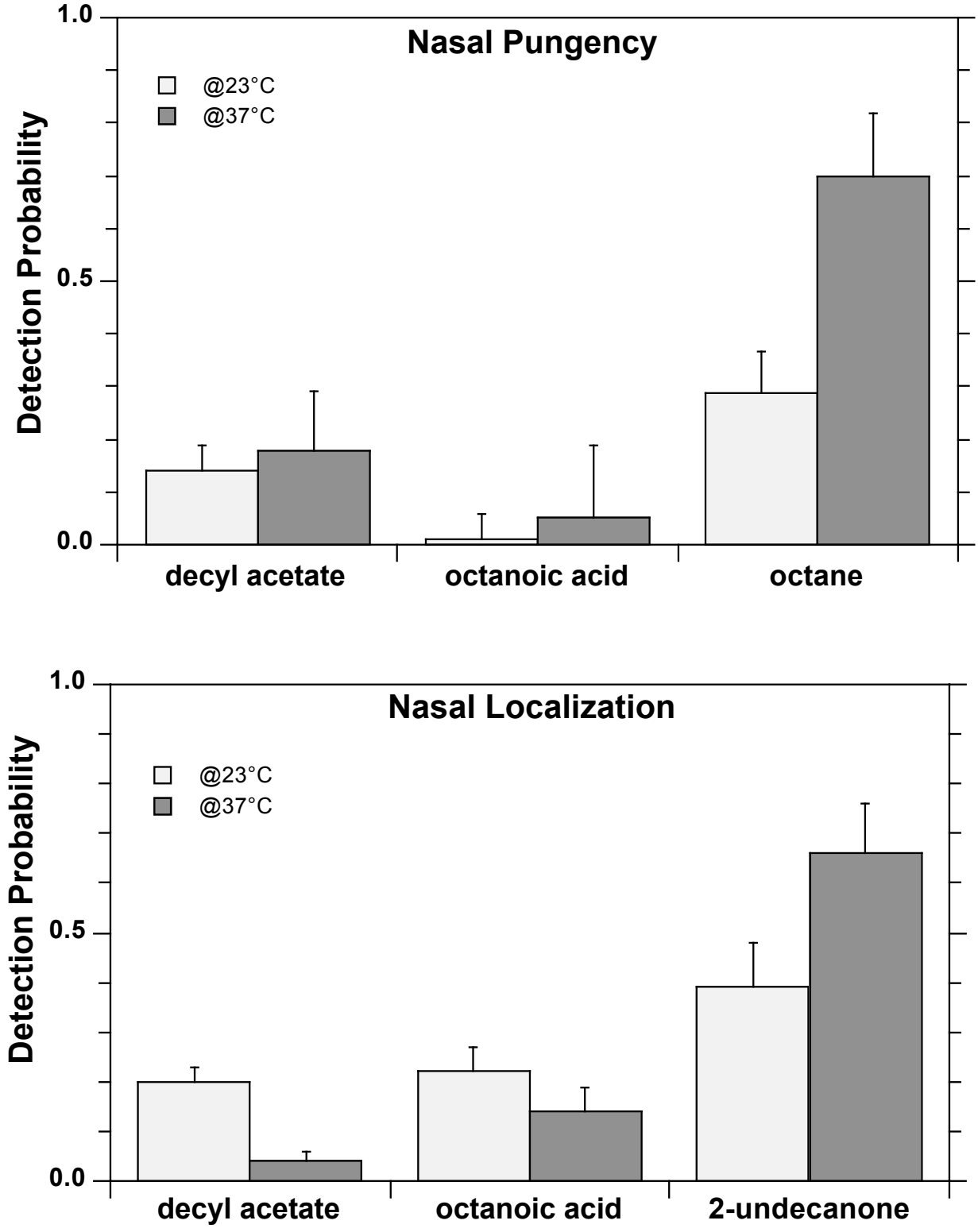

n-Alcohols
Vapor Concentration (log ppm)
6.0
4.0
2.0
0.0
0
2
4
6
8
10
12
Carbon Chain Length
Saturated Vapor @ 37°C
Saturated Vapor @ 23°C
Measured NPT
Calculated NPT

FIGURE 4


Nasal Pungency
@23°C
@37°C
Detection Probability
1.0
0.5
0.0
decyl acetate
octanoic acid
octane
Nasal Localization
@23°C
@37°C
Detection Probability
1.0
0.5
0.0
decyl acetate
octanoic acid
2-undecanone

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