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Section 3.7

Physicochemical Basis for Odor and Irritation Potency of VOCs

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3.7.1 The sensory receptors for olfaction and chemesthesis

Our awareness of the presence of airborne chemicals around us relies principally on two sensory systems: olfaction and chemesthesis (also known as the common chemical sense, see Green and Lawless 1991, Green et al. 1990). The sense of smell gives rise to the perception of odors whereas chemesthesis gives rise to the perception of what we like to call pungent sensations or pungency. These sensations include tingling, piquancy, burning, freshness, prickling, irritation, stinging, and the like.

Smell is mediated by the olfactory nerve (cranial nerve I). The olfactory receptor cells are neurons present in the olfactory epithelium, a small patch of tissue located in the extreme upper back portion of the nasal cavity (Figure 1, right side). Most of the epithelium covering the rest of the nasal cavity is respiratory epithelium. Olfactory receptor neurons (ORN) constitute, then, a portion of nervous tissue in direct contact with our environment. From one end, the bipolar ORNs send a dendrite to the surface of the epithelium where it ends in an olfactory vesicle with protruding cilia immersed in the mucus covering the epithelium. From the other end, ORNs send an axon that joins other axons from neighboring cells to form the olfactory nerve. The nerve runs through perforations on the cribiform plate of the ethmoid bone and reaches the olfactory bulb where they make the first synapse of the pathway within structures called glomeruli. From there, the olfactory pathway continues to a number of higher centers in the central nervous system.

Chemesthesis on the mucosae of the face (nasal, ocular, and oral) is principally mediated by the trigeminal nerve (cranial nerve V). The reception structures for facial chemesthesis are free nerve endings from sensory branches of the trigeminal nerve (Figure 1, left side). It is believed that polimodal nociceptors on those nerve endings are principally responsive for their chemical sensitivity (Silver and Finger 1991). Thus, chemesthesis is closely related to the somatic sensory system, particularly pain. Nociceptors are present in nerve endings of axons belonging to C and Aδ fibers (Martin and Jessell 1991). All sensory branches of the trigeminal nerve originate on the Gasserian or semilunar ganglion.

Symptoms of nose, eye, and throat irritation figure prominently among the complaints mentioned by occupants of polluted environments (Mølhave et al. 1991), for example in the condition known as the Sick Building Syndrome (SBS) (Apter et al. 1994, Kostiainen 1995). Research on the functional characteristics and physicochemical basis of chemical sensory irritation in humans will reveal important information to understand and prevent these unwanted reactions (Cometto–Muñiz and Cain 1992).

3.7.2 Functional separation of odor and irritation

The independent study of olfaction and nasal irritation is hampered by the fact that virtually all volatile compounds can stimulate both sensory systems (cf. Cometto-Muñiz et al. 1989). It all depends on the dose, as a central axiom in toxicology states. At low concentrations of inhaled chemicals, only odor is apparent. As the concentration increases, pungency begins to join in (see Cometto-Muñiz and Hernández 1990). The critical issue entails defining the boundary between a purely olfactory response and an olfactory plus chemesthetic response, and then relating those responses back to relevant properties of the chemical stimulus. Given these considerations it is difficult to assess nasal pungency thresholds in subjects with a normal sense of smell (i.e., normosmics) since they would have to judge when a sensation becomes barely pungent in the context of an often quite strong odorous background. In order to dissect the olfactory from the trigeminal threshold response to volatile organic compounds (VOCs) we have resorted to: 1) use of subjects with no olfaction (i.e., anosmics), 2) measurement of eye irritation thresholds, and 3) measurement of nasal localization thresholds. The response of eye irritation is mediated by the trigeminal nerve. The response of nasal localization, or lateralization, entails the ability to determine which nostril (left or right) received a chemical vapor and which one plain air upon simultaneous stimulation. Nasal localization is also mediated by the trigeminal nerve.

Use of anosmic subjects

Some individuals, for one or another reason, have never had or have lost their sense of smell. They are called anosmics. This condition may be permanent or temporary. In the studies of homologous chemical series described below (that is, studies of series of compounds sharing a common chemical functional group, for example, alcohols) we have resorted to test congenital and head-trauma anosmics due to the stability of their anosmic condition. Congenital anosmics are persons that were never able to smell, as far as they can remember, with no history of any particular event that might have caused their anosmics are persons that lost their olfactory sense after a blow to the head. Although a percentage of these patients recover their olfaction partially or totally, if improvement has not occurred within 6 to 12 months after the trauma it is unlikely that it will occur at all (Costanzo and Zasler 1991). Other pathologies can also produce anosmia (see Cain et al. 1988) but might do it only on a temporary or recurring basis.

In our studies of the sensory properties of homologous chemical series we have measured **odor thresholds** in **normosmics**, i.e., subjects with a normal sense of smell, and have measured **nasal pungency thresholds** in **anosmics**, for whom odor would not interfere. To select normosmic and anosmic participants we have used the Connecticut Chemosensory Clinical Research Center (CCCRC) test of olfactory function (Cain 1989).

Measurement of eye irritation thresholds

Although avoidance of odor biases provided a strong rationale for the study of anosmics, it was not guaranteed that their nasal pungency thresholds reflected the true trigeminal sensitivity of normosmics. An alternative way to look at the chemesthetic stimulation potency of chemicals in normosmics and, at the same time, to avoid olfactory interference, consisted in measuring **eye irritation** thresholds. The trigeminal nerve also provides the ocular mucosa with chemical sensitivity.

Eye irritation thresholds measured in normosmics were compared with nasal pungency thresholds measured in anosmics, using the same representative members of various chemical series, identical psychophysical procedure, and a similar stimulusdelivery technique (Cometto-Muñiz and Cain 1995). The outcome showed that, overall, both thresholds fell close to each other (Figure 2). This suggested a similar chemesthetic sensitivity in both mucosae, though it was interesting to find that, for more than one series, the eye continued to respond to members for which the nose had sometimes failed to respond, for example: 1-octanol, octyl acetate, and geraniol (see Figure 2). It was later shown that eye irritation thresholds for homologous alcohols (Cometto-Muñiz and Cain 1998) and selected terpenes (Cometto-Muñiz et al. 1998b) are virtually identical in normosmics and anosmics (Figure 3), supporting the notion that anosmics do not have any significant trigeminal sensory impairment in the ocular mucosa compared to normosmics.

Insert Figures 2 and 3 about here

Measurement of nasal localization thresholds

Early investigations suggested that human subjects, via their sense of smell, could tell which nostril received a chemical stimulus when a puff of air entered one nostril and, simultaneously, the chemical entered the other (von Bèkesy 1964). Later, it was demonstrated that such nasal localization (or lateralization) was possible not through olfaction but through nasal chemesthesis, that is, through activation of the trigeminal nerve (Kobal et al. 1989, Schneider and Schmidt 1967). This phenomenon provided an opportunity to look at the comparative sensitivity of nasal chemesthesis in normosmics and anosmics.

Recent studies employing homologous alcohols (Cain and Cometto-Muñiz 1996, Cometto-Muñiz and Cain 1998) and selected terpenes (Cometto-Muñiz et al. 1998b) have revealed marginally lower nasal localization thresholds in normosmics compared to anosmics, but the difference failed to achieve significance (Figure 4). Thus, any difference in nasal chemesthetic sensitivity between normosmics and anosmics, if real, appears small. Altogether, the data suggests that nasal detection (i.e., nasal pungency) thresholds in anosmics or nasal localization thresholds in either group do indeed reflect the concentration at which a substance starts to elicit a trigeminal response in subjects with normal olfaction. It, then, seems that trigeminal sensitivity is similar between normosmics and anosmics both in the ocular and in the nasal mucosa.

Insert Figure 4 about here

3.7.3 Chemosensory detection thresholds along chemical series

The strategy of separating the olfactory from the trigeminal response to airborne chemicals via testing anosmics, testing eye irritation, and testing nasal localization, was complemented by an orderly selection of the substances to study. Firstly, we were interested in selecting compounds proven to be ubiquitously present indoors (Brown et al. 1994, Wolkoff and Wilkins 1993). Secondly, given the broad chemical diversity of those compounds, we needed to systematize their investigation in order to facilitate the extraction of physicochemical trends from the observed sensory potency trends. To that effect we began a systematic study of the sensory properties of homologous chemical series where physicochemical properties change orderly from one member to the other and where carbon chain length constitutes a convenient "unit of change".

Aliphatic alcohols

Among the substances studied were the aliphatic primary n-alcohols (Cometto-Muñiz and Cain 1990) and a few aliphatic secondary and tertiary alcohols (Cometto-Muñiz and Cain 1993). Figure 5 shows that both nasal thresholds, odor and pungency, tended to decline with increasing carbon chain length of the n-alcohols, a tendency that will be repeated on all series tested. Odor thresholds declined at a higher rate than pungency thresholds. Nasal pungency thresholds reached a "cut-off" point within the homologous alcohols where the ability of a homolog to evoke pungency began to fade. This occurred at the level of 1-octanol for which the anosmics, as a group, failed to reach a pungency threshold in 25% of instances. Switching the alcohols functional group (HO⁻) to a secondary carbon (1-propanol to 2-propanol, 1-heptanol to 4-heptanol, and 1-butanol to sec-butanol) or to a tertiary carbon (1-butanol to tert-butanol) raised both the odor and pungency thresholds. Figure 5 also reveals two features that will be repeated on all series tested: 1) The difference between normosmics and anosmics was not simply an artifact of averaging since there was no overlap of thresholds between any single normosmic and any single anosmic for any stimulus. 2) Variability in odor thresholds (i.e., among normosmics) was much higher than in nasal pungency thresholds (i.e., among anosmics), as shown by the size of the standard deviation (SD) bars. In most cases variability among anosmics was so low that the SD bar is hidden by the plot symbol.

Insert Figure 5 about here

Acetate esters

Figure 6 shows odor and nasal pungency thresholds for homologous n-acetate esters and a couple of branched homologs (Cometto-Muñiz and Cain 1991). Similarly to the outcome for n-alcohols, both thresholds declined with carbon chain length, odor thresholds declined at a higher rate than pungency thresholds (at least for the first four homologs), there was no overlap between both types of thresholds (see SD bars), and odor threshold variability was higher than that for pungency. In addition, odor thresholds tended to reach a plateau after butyl acetate whereas pungency thresholds showed a cut-off at octyl acetate which failed to be detected by two of the four anosmics. Decyl and dodecyl acetate failed to be detected by three of the four anosmics. The branched butyl acetates (sec and tert) did not show a robust or systematic increase or decrease in their thresholds compared to the unbranched homolog.

Insert Figure 6 about here

<u>Ketones</u>

Thresholds for the ketone series are presented in Figure 7 (Cometto-Muñiz and Cain 1993). Most trends in thresholds common to alcohols and acetates, as listed in the

previous paragraph, continued to hold for the ketones. Here, both odor and nasal pungency thresholds reached a plateau at the level of 2-heptanone, and there was no cut-off effect in pungency at least up to the highest homolog tested, 2-nonanone.

Insert Figure 7 about here

Alkylbenzenes

Figure 8 depicts odor and pungency thresholds for the alkylbenzenes (Cometto-Muñiz and Cain 1994b). Many of the features seen for n-alcohols, n-acetates, and ketones were also seen here (e.g., decline of both kinds of threshold with carbon chain length, larger variability for odor thresholds, no overlap between both threshold types) but, in the alkylbenzenes, the plateau in odor thresholds and the cut-off in pungency thresholds began very early in the series: both effects appeared at the level of propyl benzene.

Insert Figure 8 about here

Aliphatic aldehydes

Thresholds for aliphatic aldehydes are shown in Figure 9 (Cometto-Muñiz et al. 1998a). As with all previous series, we see that odor and pungency thresholds declined with carbon chain length, odor thresholds were more variable (as reflected in larger SD bars), and there was absolutely no overlap in thresholds between individual subjects in the normosmic group and those in the anosmic group. The gap between odor and pungency remained relatively uniform between 4 orders of magnitude for butanal and pentanal, and 5.6 orders of magnitude for octanal. A cut-off for nasal pungency

appeared at the level of octanal since two of the four anosmics failed to detect this compound in some instances.

Insert Figure 9 about here

Carboxylic acids

Figure 10 shows odor and nasal pungency thresholds for carboxylic acids (Cometto-Muñiz et al. 1998a). It can be seen that all the usual features of odor and pungency thresholds along homologous series, summarized in the previous paragraph, also hold for the acids. The gap between odor and pungency grew from 1.6 orders of magnitude for formic acid to 5.2 orders of magnitude for octanoic acid. A cut-off for nasal pungency began to appear with hexanoic acid, where one of the four anosmics consistently failed to detect it.

Insert Figure 10 about here

Selected terpenes

In a recent investigation we have departed from the study of homologous series and chose to study a group of terpenes and the structurally related compound cumene (Cometto-Muñiz et al. 1998b). The selected terpenes provided an opportunity to look at structure-activity relationships in sensory responses to chemicals from a slightly different view, including the effects of structural isomerism, e.g., linalool ($C_{10}H_{18}O$) vs. geraniol ($C_{10}H_{18}O$), and optical isomerism, e.g., R(+)limonene vs. S(-)limonene, on olfactory and chemesthetic thresholds. Figure 11 presents odor and nasal pungency thresholds for the substances tested, and shows that, for a number of them, nasal pungency thresholds could not be consistently elicited.

Insert Figure 11 about here

3.7.4 <u>Description and prediction of chemosensory thresholds via physicochemical</u> properties

Using data reported in the literature, Devos et al. (Devos et al. 1990) have compiled, standardized, and averaged human olfactory thresholds for 529 compounds. There is a significant correlation (r = 0.75, p << 0.01) between our odor thresholds and the average values from the Devos et al. compilation, for the 45 compounds common to both sources (Figure 12). Our thresholds, spanning a range of 9 orders of magnitude, offer better resolution across compounds than the averages from the compilation, which span over 5 orders of magnitude. Most likely, averaging across studies accounts for much of the constriction in range in the compiled data. On average, our thresholds, representing the point of 100% detection, lie one order of magnitude above those from the compilation, which presumably represent the points of 50% or 75% detection. Our data comprise one of the largest sets obtained using a uniform methodology, procedure, and instructions on small but intensively tested groups of subjects. The approach gives the whole data set a robust internal cohesion when making comparisons across compounds, and provides a solid basis to derive physicochemical determinants of sensory potency among VOCs, for example, in the form of quantitative structure-activity relationships (QSAR) (Abraham et al. 1996, Abraham et al. 1998a, Abraham et al. 1998b).

The results for homologous series presented in Figures 2, and 5 through 10 show clearly the importance of lipophilicity in sensory potency. As each of these series progresses, the members become less water-soluble and more lipid-soluble. The concomitant sensory result is a decrease in the threshold concentration or, in other words, an increase in sensory potency. This holds for both the olfactory and the trigeminal responses. The increase in potency does not continue indefinitely, and comes to an end differently for odor than for nasal pungency. In most series, odor thresholds tend to reach a plateau or, at least, to slow down their rate of decrease. Nasal pungency thresholds, instead, reach a cut-off point from where on pungency fails to be elicited with certainty.

Recently, a particular type of QSAR based on a solvation model approach (Abraham 1993a, Abraham 1993b) has been used to reveal the physicochemical parameters that best explain the sensory results obtained. The solvation equation contains a maximum of five physicochemical descriptors: excess molar refraction (R_2) , dipolarity/polarizability (π_2^{H}), overall or effective hydrogen-bond acidity ($\Sigma \alpha_2^{H}$), overall or effective hydrogen-bond basicity $(\Sigma \beta_2^H)$, and gas-liquid partition coefficient on hexadecane at 298K (L¹⁶). Application of the solvation equation to our odor thresholds has had only moderate success (Abraham 1996), leaving a relatively large amount of unexplained variance: about 20%, although no other odor QSAR model has done better than this (see Cometto-Muñiz et al. 1998a). The solvation equation applies only to "transport" processes, that is, those in which either the distribution of a solute between phases or the rate of transfer of a solute from one phase to another forms the key step. The equation does not apply to processes where the key step is a specific stimulusreceptor interaction. In the present case, the solute refers to the odorant stimulus, and the phases involved are the various biophases through which the stimulus travel on entering the nose: different mucus layers, membrane of olfactory neurons, interstitial

fluid, etc. The modest performance of the solvation model when applied to odor thresholds suggests that the olfactory response relies only partially on stimulustransport processes, and that certain key steps must rely on more restricted and specific odorant-receptor interactions, like those derived from size and shape of the molecule. This suggestion is in line with preliminary data indicating that addition of a new descriptor that is a function of the maximum length of the molecule can improve the robustness of the solvation equation for odor (Abraham et al. 1997).

In contrast to the odor case, the solvation equation has done very well to describe and predict nasal pungency (Abraham et al. 1996, Abraham et al. 1998a) and eye irritation (Abraham et al. 1998b) thresholds, that is, the two responses mediated by the trigeminal nerve. The success of the equation indicates that these chemesthetic responses in the face do rely heavily on transport processes that carry the airborne irritant from the vapor-phase to the biophase where trigeminal nerve activation takes place. The most updated version of the equation for nasal pungency (Abraham et al. 1998a) reads as follows:

$$\begin{split} &\log{(1/\text{NPT})} = -8.519 + 2.154 \ \pi_2^H \ + 3.522 \ \Sigma \alpha_2^H \ + 1.397 \ \Sigma \beta_2^H \ + 0.860 \ \text{log} \ \text{L}^{16} \\ &n = 43 \qquad r^2 = 0.955 \qquad \text{sd} = 0.27 \qquad F = 201 \end{split}$$

where 1/NPT is the reciprocal of the nasal pungency threshold (NPT) in ppm, n is the number of data points (VOCs), r is the correlation coefficient, sd is the standard deviation in log 1/NPT, and F is the F-statistic. The four physicochemical descriptors $(\pi_2^{H}, \Sigma \alpha_2^{H}, \Sigma \beta_2^{H}, L^{16})$ are as defined above. The descriptor R₂ is absent since it did not achieve statistical significance. In turn, the equation for eye irritation (Abraham et al. 1998b) reads as follows:

 $\log (1/\text{EIT}) = -7.918 - 0.482 \text{ R}_2 + 1.420 \text{ } \pi_2^{\text{H}} + 4.025 \text{ } \Sigma \alpha_2^{\text{H}} + 1.219 \text{ } \Sigma \beta_2^{\text{H}} + 0.853 \text{ } \log \text{ } \text{L}^{16}$

where 1/EIT is the reciprocal of the eye irritation threshold (EIT) in ppm and all terms and descriptors are as defined above.

We have mentioned that the results illustrated in Figures 2, and 5 to 10 point out the importance of lipophilicity for sensory potency. The QSAR analysis confirms the outcome since the term that reflects the lipophilicity of the stimulus, that is, the descriptor L¹⁶ (the gas-liquid partition coefficient on hexadecane at 298K), accounts for 52% of the variation on odor thresholds, 55% of the variation on nasal pungency thresholds and 63% of the variation on eye irritation thresholds, in the respective equations. Nevertheless, lipophilicity cannot explain the appearance of the cut-off point in nasal pungency. At least two mechanisms may account for such cut-offs (Franks and Lieb 1990): a purely physical mechanism whereby the maximum available quantity of vapor-phase stimulus falls below the threshold, and a biological mechanism whereby the stimulus lacks a key property to trigger reception or transduction. For example, beginning at a certain point in a homologous series the molecules could become too large to interact effectively with a target site or to fit into a binding pocket of a carrier or a receptive macromolecule. Comparison of data predicted by the nasal pungency solvation equation listed above with experimental data and physicochemical data (e.g., saturated vapor concentration) can help to distinguish between the two mechanisms (Cometto-Muñiz et al. 1998a).

3.7.5 <u>Chemosensory detection of mixtures</u>

Occupants of indoor spaces are exposed to dozens, perhaps even hundreds, of VOCs. Sensory irritation in buildings does not seem to come about only from frank

irritants, such as formaldehyde. It appears, instead, that irritation might arise from the aggregate effects of many VOCs with different degrees of chemical reactivity. The extent to which mixtures of VOCs can evoke agonistic effects in olfaction and chemesthesis becomes, then, an important issue.

The outcome from studies of homologous chemical series has shown, in every case, that the larger homologs (e.g., 2-heptanone), not usually considered particularly irritating compared to the smaller homologs (e.g., acetone), have, in fact, a stronger sensory potency due to their much lower odor and nasal pungency thresholds. Keeping this observation in mind, a recent study (Cometto-Muñiz et al. 1997) explored possible agonistic sensory effects among the components of five different mixtures: Two of them had three components, two had six components, and the last mixture had nine components. One of the three-component mixtures and one of the six-component mixtures contained relatively small homologs from different series, the other three- and six-component mixtures contained larger homologs from different series. The ninecomponent mixture contained both small and large homologs, also from different chemical series. The results showed that the mixtures achieved threshold when none of the components had reached its individual threshold concentration, indicating the existence of agonism among chemicals. The degree of agonism tended to increase with number of components and with the lipophilicity of such components (as a rule, larger homologs, having long carbon chain lengths, are more lipophilic than smaller homologs, having short carbon chain lengths). Overall, agonism was stronger for the chemesthetic modalities, particularly eye irritation, than for the olfactory modality.

Another recent investigation (Cometto-Muñiz et al. 1999) focused on the binary mixture of 1-butanol and 2-heptanone, but studied it in detail by varying the relative ratios of the two components in a systematic way. Also, instead of measuring thresholds according to a fixed criterion of performance, the study measured, for the two single chemicals and their various mixtures, complete detectability functions spanning the range from chance detection to virtually perfect detection. Again, the outcome indicated the presence of agonism for all three sensory endpoints explored: odor, nasal pungency, and eye irritation.

3.7.6 Needs for further research

From a methodological perspective, in order to advance our knowledge of the physicochemical basis for the odor and irritation potency of VOCs, we need to understand the role that different chemical-delivery techniques play in the sensory results obtained. In the simplest systems, the tested vapor(s) is(are) presented from an enclosed container to the nose or eyes. There are many examples of this design, one of them being the "squeeze bottles" (Cain 1989). The technique can be compared to what in olfactory studies is called "static" olfactometry (Cain et al. 1992). Use of face masks fed from small chambers that contain the chemical stimulus (or stimuli) constitute the next level of complexity for delivery systems. Here, the vapor(s) flows carried by a dilution gas, generally odorless air, towards the face of the subject. The procedure resembles what in olfactory studies is called "dynamic" olfactometry (Cain et al. 1992). Finally, whole-body environmental chambers constitute the most representative system for obtaining environmentally realistic sensory responses to VOCs. Preliminary data indicate that sensory thresholds decrease as we move from squeeze bottles to face masks and from them to whole-body chambers. Issues of cost, ease of use, and pace of experimentation call for the selection of simple and versatile systems for sensory testing whose results can be extrapolated to those of environmental chambers. Future research should clarify the relationship among sensory responses — particularly thresholds obtained with these various techniques, and establish the generality of such relationship across chemicals.

Another important topic for further research is a systematic study of mixtures (Cometto-Muñiz et al. 1999, Cometto-Muñiz et al. 1997). We need to understand the role that number of components and chemical identity of such components play in the sensory responses to mixtures, in particular at concentrations near detection thresholds for odor, nasal pungency, and eye irritation. Given the large number and variety of VOCs present indoors, this task seems enormous. Perhaps a productive approach might consist on the initial detailed study of very simple mixtures, i.e., binary, ternary, quaternary, combined with a realistic physicochemical modeling. The model should ideally possess descriptive ability for tested substances, predictive ability for untested substances, and ability to adjust incrementally, providing more accurate predictions, as data for new substances are incorporated.

All the results discussed in this article represent short-term (1–3 sec) exposures. Nevertheless, indoor exposures linger for days, months, and even years. It has been shown that odor sensations fade quite rapidly with time (adaptation) whereas chemesthetic sensations can build up for 30 or more minutes (temporal integration or summation) before adaptation begins to be produced (Cain et al. 1986, Cometto-Muñiz and Cain 1984, Cometto-Muñiz and Cain 1994a). Understanding the time-course of these sensory responses over long periods of time represents another challenge for future studies on indoor air.

Summary

It is widely acknowledged that among the likely causes for building-related complaints, the aggregate effect of a variety of VOCs deserves particular attention (Apter et al. 1994, Hodgson et al. 1994, Kostiainen 1995, Rothweiler and Schlatter 1993). Among the various symptoms evoked, sensory irritation not only figures prominently but also lends itself to psychophysical measurement in humans (Cometto-Muñiz and Cain 1992, Hudnell et al. 1992, Kjærgaard et al. 1992, Mølhave et al. 1991).

Our lab has a particular interest in studying the functional characteristics of the senses of smell and sensory irritation in humans (Cometto-Muñiz and Cain 1992, Cometto-Muñiz and Cain 1996). Our approach entails a stimulus-strategy and a response-strategy. From the perspective of the stimulus we have chosen to test families of chemicals, typically homologous series (e.g., acetate esters) but also more diverse groups (e.g., terpenes). Homologous series provide a convenient "unit of change", represented by carbon chain length, along which physicochemical properties change in an orderly fashion, allowing to relate those changing properties with the sensory outcome. From the perspective of the nose by testing subjects lacking olfaction, i.e., anosmics, for whom odor does not interfere. The applicability to normosmics of the nasal trigeminal responses obtained from anosmics was initially suggested by the similarity of eye irritation thresholds in both groups, and further supported by the similarity of nasal localization thresholds in both groups (Cometto-Muñiz and Cain 1998).

In the studies described, use of a uniform sensory methodology, procedure, and instructions in a small but intensively tested group of subjects has been combined with selection of a wide range of VOCs relevant to indoor air. The results have permitted to build a strong QSAR, based on a solvation model, that describes and predicts nasal pungency and eye irritation thresholds for VOCs using a maximum of five general physicochemical descriptors (Abraham et al. 1998a, Abraham et al. 1998b). Modeling of odor thresholds via the solvation equation has been less successful. This can be taken as an indication that some key steps on the odorant-receptor interaction rely on more specific stimulus properties than those reflected on the five general physicochemical descriptors. Finally, we discuss the outcome of experiments comparing the sensory impact of VOCs presented singly and in mixtures of up to nine components. The results showed various degrees of agonism among the components of the mixtures. Such agonism allowed detection of the mixtures when their constituents were present at concentrations below their individual thresholds. As the number and the lipophilicity of the components increased, so did their degree of agonism.

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Figure Legends

Figure 1. Left. Innervation of the ocular, nasal, and oral mucosa by branches of the trigeminal nerve. From Silver and Finger, 1991. <u>Right</u>. Showing the olfactory region of the nasal cavity (hatched area) innervated by the olfactory nerve. From Mygind et al., 1982.

<u>Figure 2</u>. Comparison of nasal pungency (filled squares, continuous lines) and eye irritation (triangles, broken lines) thresholds for homologous alcohols, acetates, ketones, alkylbenzenes, selected terpenes and cumene. Bars indicating standard deviations are sometimes hidden by the symbol.

<u>Figure 3</u>. Comparison of eye irritation thresholds in normosmics (empty circles, continuous lines) and anosmics (filled circles, broken lines) for homologous alcohols, cumene and selected terpenes. Bars indicating standard deviations are sometimes hidden by the symbol.

<u>Figure 4</u>. Comparison of nasal localization thresholds in normosmics (empty circles, continuous lines) and anosmics (filled circles, broken lines) for homologous alcohols, cumene and selected terpenes. Bars indicating standard deviations are sometimes hidden by the symbol.

Figure 5. Odor (empty circles) and nasal pungency (filled circles) thresholds for homologous alcohols. Only n-homologs are joined by a line. The broken line shows the homolog for which pungency begins to fade (1-octanol) producing a cut-off effect in the series (see text). Bars indicating standard deviations are sometimes hidden by the symbol. Figure 6. Odor (empty circles) and nasal pungency (filled circles) thresholds for homologous acetates. Only n-homologs are joined by a line. The broken line shows the homolog for which pungency begins to fade (octyl acetate) producing a cut-off effect in the series (see text). Bars indicating standard deviations are sometimes hidden by the symbol.

<u>Figure 7</u>. Odor (empty circles) and nasal pungency (filled circles) thresholds for homologous ketones. Bars indicate standard deviations.

<u>Figure 8</u>. Odor (empty circles) and nasal pungency (filled circles) thresholds for homologous alkylbenzenes. Bars indicating standard deviations are sometimes hidden by the symbol.

Figure 9. Odor (empty circles) and nasal pungency (filled circles) thresholds for homologous aldehydes. The broken line shows the homolog for which pungency begins to fade (octanal) producing a cut-off effect in the series (see text). Bars indicating standard deviations are sometimes hidden by the symbol.

<u>Figure 10</u>. Odor (empty circles) and nasal pungency (filled circles) thresholds for homologous carboxylic acids. The broken line shows the homolog for which pungency begins to fade (hexanoic acid) producing a cut-off effect in the series (see text).

Figure 11. Odor (empty circles) and nasal pungency (filled circles) thresholds for selected terpenes and cumene. Out of 32 instances of measurement across four anosmics, the pinenes, the limonenes, gamma-terpinene, and geraniol failed to reach a nasal pungency threshold in most instances, p-cymene failed in 56% of instances, linalool failed in 31% of instances, and cumene failed in 22% of instances. Delta-3-carene and 1,8-cineole virtually never failed to evoke a nasal pungency threshold in the anosmics.

Figure 12. Comparison between our odor thresholds (Cometto-Muñiz and Cain 1990, Cometto-Muñiz and Cain 1991, Cometto-Muñiz and Cain 1993, Cometto-Muñiz and Cain 1994b, Cometto-Muñiz et al. 1998a, Cometto-Muñiz et al. 1998b), sorted in descending order, and those compiled, standardized, and averaged by Devos et al. (Devos et al. 1990). The correlation between both sets is high and significant (r=0.75, n=45, p<<0.01).

















Figure 7



FIGURE 8





FIGURE 10



FIGURE 11





FIGURE 12