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Influence of Airborne Contaminants on Olfaction and the Common Chemical Sense

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Introduction

The detection by humans of chemical substances in the environment relies on two sensory channels: olfaction and the common chemical sense. The olfactory nerve - cranial nerve I - subserves the perception of odors whereas the trigeminal nerve - cranial nerve V - subserves the perception of pungency or common chemical sensations. Pungency comprises a number of sensory impressions that arise in mucosal tissue - particularly conjunctival, nasal, oral, and pharyngeal -, sensations which, in the case of the last three loci, are not properly odors or tastes. **Pungency** involves irritation, prickliness, burning, tingling, piquancy, freshness, and stinging, among other quality descriptors. The use of the almost odorless [34] and tasteless stimulus carbon dioxide (CO_2) to provoke pungency has served very well in the past to study both nasal and oral pungency with the same, relatively harmless substance [41, 46, 48, 56, 65, 111].

As will be detailed in the next section, there are specialized anatomical structures - the olfactory neurons - that deal with the detection of odorant molecules. In contrast, ocular and oro-nasal pungency arises from the stimulation by chemicals - directly or indirectly - of free nerve endings from the trigeminal nerve.

I Morphological effects of airborne contaminants on nasal sensory and respiratory epithelium.

- Normal histology

The nasal cavity is the first barrier which inhaled substances face upon entering the body. Three general types of epithelium provide the lining of the cavity: squamous, respiratory, and olfactory. The olfactory region is restricted to a small area in the most upper back portion of the cavity (Figure 1). The proportion of air reaching this region in normal inspiration is about 5 %, and can be increased up to 20 % when sniffing [49].

Insert Figure 1 about here

The area covered by the squamous and respiratory epithelium presents various epithelial cell types. As the air enters the nose, it passes through a zone of squamous epithelium, a zone of transitional (or intermediate) epithelium, and then a zone of pseudostratified columnar epithelium with an increasing number of ciliated cells [94]. Being a mucociliary apparatus, the system also has goblet cells and seromucus producing glands [117]. The nasal tissues are very richly vascularized and highly innervated. Nerves supply the blood vessels and the nasal glands, and provide mechanical and common chemical sensitivity [38]. These sensitivities are mediated by free nerve endings of the ophthalmic and maxillary divisions of the trigeminal nerve (Cranial Nerve V).

The olfactory mucosa contains neurons - responsible for the detection of odors - and two other cell types: sustentacular or supporting cells and basal cells (Figure 2). An **olfactory neuron** sends a single dendritic process to the surface of the epithelium where it ends in an olfactory vesicle with protruding cilia immersed in the mucus layer covering the epithelium surface. At the opposite end of the neuron, a single axon is sent and joins other axons from neighboring receptors to form bundles wrapped in myelin sheets. These bundles run through the perforations of the cribriform plate of the ethmoid bone and reach the glomerular zone of the olfactory bulb where the fibers make the first synapse of the pathway.

Insert Figure 2 about here

In summary, unlike any other sensory system, the olfactory receptors are neurons themselves - not epithelial cells - so the stimulating molecules impinge directly on the neurons whose axons form the olfactory nerve (Cranial Nerve I). Consequently, no synapse intervenes between the receptor and the nerve fibers of the olfactory nerve that transmit the information to the olfactory bulb. This anatomical arrangement means that any material that penetrates the olfactory receptor wall will be transported into the brain along the olfactory cell axon. Also unlike any other mature neural tissue, olfactory neurons proliferate continuously throughout the life of the organism and may regenerate after injury [67, 91].

The **sustentacular** (or **supporting**) cells of the olfactory mucosa form tight junctions with the receptors cells. They posses a microvillous border (see Figure 2) in contact with the mucus bathing the epithelium. The **basal** cells lie at the bottom of the epithelium and form the stem cells for the neurons.

An important difference between the cilia of the cells in the respiratory epithelium and the cilia of the olfactory receptors should be pointed out. The former posses active motion and beat in an undulating manner, whereas the latter apparently lack inherent motility, being irregularly moved by the air currents in the nose and providing, perhaps, only a stirring action of the mucus [88].

Bowman's glands - also called olfactory glands - are located at the level of the lamina propria in the olfactory epithelium. They extend narrow ducts perpendicular to the layer of olfactory and supporting cells to the epithelial surface. Through these ducts the glands release secretions. At present it is believed that the serous or watery component of the mucus comes from the Bowman's glands while the viscous component originates in the supporting cells [115].

The **mucus** layer most likely plays an important role in the process of odor detection [66]. As will be detailed in Section II, the mucus layer consists of two distinct phases: an external more viscous layer floating over an internal more watery fluid. Odorants entering the nose and reaching the olfactory region penetrate these

layers according to their air-(viscous) mucus partition coefficient and, then, they reach the receptors in an amount proportional to their (watery) mucus-lipid partition coefficient, since the membrane of the cilia of the olfactory neurons is basically, as almost any other biological membrane, a lipid bilayer. These physicochemical considerations need to be taken very much into account when estimating the effective concentration necessary to elicit olfactory responses from different substances. For different odorants, the concentration reaching the receptors might bear a dissimilar relationship to the concentration entering the nose.

- Acute and subacute nasal toxicity

Since the nasal cavity is normally in continuous direct contact with the air in the environment, it is prepared to take challenges from potentially harmful airborne substances. Almost all of the work done in this realm has employed laboratory animals, principally rodents, to test the acute effects of noxious air contaminants.

As Jiang [73] points out, several stages of modification can be seen in the nasal passages as a response to different levels of challenges. When the defenses are overcome, degenerative changes are triggered, leading to inflammation and subsequent repair. If the exposure continues, adaptive or defensive responses (e.g. squamous metaplasia or globet cell hyperplasia) may start. The repair process usually involves cell proliferation to replace erosions or ulcerations

of damaged tissue. Excessive proliferation might, in turn, result in hyperplasia or neoplasia.

The squamous epithelium is generally the least affected by gaseous irritants. Nevertheless, at high enough concentrations of the contaminant, erosions or ulcerations, usually focal, are produced.

In the respiratory epithelium, a gradient of damage can be produced depending on the severity of the exposure. According to Jiang [73], the mildest effects involve loss of cilia, which may be produced over extensive areas, with minimal changes in the underlying epithelial cells. This probably depends on continued mucus flow over the surface of such cells. More drastic exposures lead to degeneration of epithelial cells, cell separation, and exfoliation. The basement membrane might remain intact, though more severe lesions could result in ulceration. If the challenge is not repeated, the damaged areas are repaired and finally covered by normal respiratory epithelium. Repeated exposures can lead to squamous metaplasia, where the normal respiratory epithelium is replaced by squamous epithelium, presumably more resistant to the toxic effects of irritants. This constitutes a common adaptive response of the nose. It is also mentioned [73] that repeated exposures can result in goblet cell hyperplasia with increased amount of altered mucus. Goblet cells are mucus producing cells present in the nasal respiratory epithelium.

As in the case of the respiratory epithelium, the olfactory epithelium can also undergo a series of transformations depending on the degree of challenge with the irritant. Lesions range from slight loss of olfactory cilia to complete destruction of certain areas of the olfactory epithelium [73]. Nevertheless, as already mentioned, olfactory neurons are capable of regeneration from basal cells and this is one of the possible repair processes. Other alternatives, depending on the extent and degree of the inflicted damage, include formation of squamous epithelium or replacement of the olfactory epithelium by ciliated respiratory epithelium. The relationship between type and severity of inflicted damage and kind of repair obtained is not yet well understood.

- Chronic toxic response

The effects of long term exposure to airborne substances have been in general studied in animal models, principally rodents. These animals are obligatory nose breathers so changes found in their noses do not necessarily correspond to what might be found in humans.

Cancer of the nose is rare in the general population. Nevertheless, in certain occupational settings various chemicals have been implicated in the production of nasal cancers. This is the case for nickel refinery workers [116, 119], and for workers exposed to dust from wood [2, 68, 87] and leather [1, 3]. High wood dust concentrations have been shown to cause mucostasis [11, 17].

Formaldehyde exposure has been involved in the production of nasal cancer [69]. Extensive studies of exposures to this chemical showed no clear evidence of an increased total mortality but did show increased mortality from malignancy in specific organs: nasopharynx, oropharynx, lymphatic system, lung, and prostate [18]. Combinations of exposure to formaldehyde and wood dust resulted in an additive carcinogenic effect in some investigations [97] but not in others [71].

Feron et al. [60] presented an in-depth account of the results obtained from chronic nasal exposures in experimental animals (mainly hamsters and rats). Tables 1 to 4 summarize these findings in terms of chronic nonneoplastic and neoplastic lesions of the respiratory mucosa as well as chronic nonneoplastic and neoplastic lesions of the olfactory mucosa.

Insert Tables 1 to 4 about here

II Functional indices of toxicity from airborne contaminants in animals.

- Mucociliary clearance

The study of mucociliary clearance has been the subject of more numerous investigations in the lower airways than in the nasal

passages. There are indications that nasal mucociliary clearance might be more resistant to the adverse effects of airborne substances than mucociliary clearance in the lower airways [63]. This should come as no surprise since one of the reputed primary functions of the upper airways is to act as a barrier to inhaled noxious substances, preventing them from reaching the vital lower portions of the respiratory tract. For this same reason the nasal cavity becomes the first target of such materials which, over time, are likely to affect it.

Here is where the importance of an efficient nasal mucociliary clearance becomes apparent since, through it, the cells underlying the airway secretions are protected from the potential deleterious effects of external materials. These secretions provide a protective layer where dust, bacteria, and other particles are trapped and then, through mucociliary clearance, carried to the glottis to be swallowed.

As mentioned in section I, there are basically three types of epithelium covering the nasal cavity: squamous, respiratory and olfactory. The mucociliary system is present in the regions lined by the respiratory epithelium although the olfactory mucosa also provides surface secretions.

Figure 3 shows a diagram of the nasal respiratory epithelium. It is nowadays recognized that the secretions covering the cells form two layers. The most superficial one is more viscous and comprises

material secreted by goblet cells and submucous glands. This region has been named the epiphase [89]. The other layer, in direct contact with the epithelial cells and were the cilia are immersed, is more watery and has been called the hypophase [89] and periciliary fluid [99]. This layer could be visualized as composed of two sublayers, the external one more fluid than the internal or mucoid one [66].

Insert Figure 3 about here

The effective functioning of the mucociliary apparatus rests on various factors: relative depths of periciliary fluid and epiphase, constitution of these secretions, as well as beating-pattern of cilia. These beat in the periciliary fluid, propelling the secretions, along with the foreign particles entangled in the viscous epiphase, over the epithelial surface. Sleigh [108] provides a detailed account of the structure and function of respiratory tract cilia.

Irritants and other airborne materials affect the functioning of this system by altering the mucus flow rate and flow patterns. As noted by Morgan et al. [89], the mechanisms by which this can be accomplished are numerous: a) changes in the viscoelastic properties and/or amount of secretions; b) tethering of the mucus to globet cells and mucus glands; c) direct toxic action of airborne substances on cilia structure or interference with ciliated cell metabolism; d) damage of ciliated cell structures by inhaled materials. Table 5 presents a brief list of potential mechanisms of

toxicity for each component of the mucociliary apparatus along with some examples, where available.

Insert Table 5 about here

- Development of tolerance to sensory irritants

As will be discussed later (section V), the development of tolerance is a phenomenon by which previous exposures to a chemical or chemicals reduce the amount of subsequent responses to the same or related agents when compared to the responses obtained from individuals not previously exposed.

Chang and Barrow [39] studied the response of rats to chlorine and formaldehyde inhalation, measuring the respiratory rate depression produced by these pungent (irritant) substances. Such a measure proved to be concentration-dependent. They explored the production of tolerance and cross-tolerance, the latter being the development of tolerance when animals are exposed to one agent and tested on the other. Results showed that tolerance development was concentration- and time-dependent and that mutual cross-tolerance existed. Both effects could be reduced with an appropriate recovery time. The authors suggested the existence of a common mechanism for tolerance and cross-tolerance development, but speculated that different reactive sites might exist for chlorine and formaldehyde at the trigeminal nerve endings.

A later study [12] sought to determine if formaldehyde pretreatment of rats would cause sensory irritation cross tolerance to other inhaled aldehydes, including saturated, unsaturated and cyclic aldehydes. Quantitation of sensory irritation response was again assessed by measuring respiratory rate depression. Results showed that cross-tolerance was produced only when testing acetaldehyde and acrolein, suggesting that the development of cross tolerance following formaldehyde pretreatment is not a general phenomenon.

- Extrapolation of animal results to estimates of permissible exposures in humans.

Alarie [4] suggested the measurement of a decrease in respiratory rate of experimental animals (specifically mice) when exposed to airborne irritants as an index of sensory irritation. For this purpose, he developed the term RD_{50} to stand for the concentration of the irritant expected to cause a 50 % decrease in respiratory rate. Figure 4 depicts recordings of respiratory rate of a mouse during room air breathing and during inhalation of an irritant.

Insert Figure 4 about here

Further investigations [5] indicated that the test could predict well which compounds would be sensory irritants for humans. In a later stage it was empirically determined that a value 0.03 times RD_{50} was a good estimate of already established Thresholds Limit Values

(TLVs) for industrial human exposure to airborne chemicals [6, 77]. The assay seemed to be valid not only for strong irritants but also for chemicals of low reactivity [96]. Table 6 lists for 40 substances values for RD_{50}, 1983 TLVs, and 0.03 RD_{50}. Figure 5 illustrates the relationship, for those same 40 compounds, between the logarithm of the 1983 TLV and the logarithm of 0.03 RD_{50}.

Insert Table 6 and Figure 5 about here

Subsequent work revealed that for substances with a low slope on the concentration-response curve (always using the decrease in respiratory rate in mice as the response) a better correlation with TLVs could be obtained by using the threshold response for sensory irritation (RD-0) multiplied by 0.2 instead of the 0.03 RD_{50} value [82, 83, 95].

A substantial number of TLVs considered in the development of OSHA regulations are based on sensory irritation. This strongly supports the need for further research on the characteristics and mechanisms of sensory irritation in both animal models and humans, emphasizing the study of appropriate ways to predict human sensory irritation from results in animals.

III Structure-activity relations in acute peripheral sensory irritation and toxicity

- Development of chemical and biophysical models to predict sensory irritation and toxicity

Very little is known about the molecular features necessary to evoke sensory irritation in the nose and upper airways. In an extensive review, Alarie [5] described several possible mechanisms concluding that reactivity of chemicals toward SH groups and ability to produce cleavage of S-S bonds in a receptor protein are more likely mechanisms than reactivity with NH_2 groups in proteins.

Nevertheless, as Alarie [5] himself recognized, there are many other sensory irritants that do not fit in the above mentioned mechanisms. These are mainly relatively nonreactive chemicals that produce pungency at much higher levels than the chemically reactive ones. A typical example of these mild irritants are the homologous normal alcohols. As a matter of fact, relatively nonreactive and only mildly irritating substances might be the most commonly encountered contaminants in occupational and environmental settings. Figure 6, taken from Nielsen and Alarie [96], depicts an hypothetical model for the reception of sensory irritants.

Insert Figure 6 about here

The probable mechanism by which mild irritants exert their action is one of a physical or physicochemical nature rather than a purely chemical one. In this regard it is interesting to bring back concepts and results of experiments on toxicity and narcosis. Back in 1939,

Ferguson [59] made a distinction between substances exerting a physiological action by chemical reactivity and those doing it by a physical mechanism. As he mentioned, even an inert substance like nitrogen at a sufficiently high pressure will induce narcosis [86]. Along with this line of reasoning, he argued that when an equilibrium exists between the external concentration of the toxic or narcotic substance and its internal concentration at the site of action, wherever it might be, the thermodynamic activity of the compound will be the same in all phases involved in the equilibrium. This would be true despite the fact that the concentrations in the various phases might be vastly different.

In practice, the thermodynamic activity of a substance in the gas phase (assuming it behaves like an ideal gas) is given by the ratio Pt/Po, i.e., partial vapor pressure of the substance at some threshold effect (e.g. a certain degree of narcosis or a pungency threshold) over the saturated vapor pressure of the substance.

As Brink and Posternak [19] pointed out, there is a rule of equal narcotic effect at equal thermodynamic activities which could be far more general than originally suggested by Ferguson [59], since it holds for substances of widely different structure and composition. There are, nevertheless, cases in which the rule does not apply. One possible cause of this deviation could rest on differences in the cells responsible for the response - e.g. olfactory neurons vs. free nerve endings - or on differences in the cell structures involved within one cell type. Another possible cause of deviation from this simple

rule could be ascribed to a superimposed effect of a chemical nature, characteristic of the particular molecule.

We believe that all these thermodynamic considerations regarding narcotic and toxic phenomena can be very well applied to stimulation of olfaction and the common chemical sense to produce odor and pungency, respectively. In this avenue of research, we repeatedly measured the detection thresholds of normal and anosmic subjects to a series of homologous normal alcohols from methanol to 1-octanol as well as to three other compounds of interest: phenyl ethyl alcohol, pyridine, and menthol [43]. Among the anosmic group, there were congenital and head trauma anosmics. The outcome for normals represented odor thresholds and that for anosmics pungency thresholds.

The results for the homologous alcohols clearly show that the enormous reduction in threshold seen in both groups with increasing carbon chain length (Figure 7) is only apparent since it is drastically reduced when thresholds are expressed in terms of thermodynamic activity (Figure 8).

Insert Figures 7 and 8 about here

This investigation has been extended to include a homologous series of esters, from methyl acetate to octyl acetate, as well as decyl and dodecyl acetates [44]. The outcome from the new series closely resembles the previous one. In both series: a) Odor and pungency

thresholds decline with carbon chain length (Figure 9). b) When expressed as percent of saturated vapor - an index of thermodynamic activity - the span of thresholds across the series is drastically reduced for both odor and pungency (Figure 10). c) Pungency thresholds - expressed as thermodynamic activity - are strikingly constant across the series (Figure 10).

Insert Figures 9 and 10 about here

Furthermore, when pungency thresholds for acetates and alcohols are plotted against saturated vapor (at room temperature) of each chemical, a single function described the data for both series (Figure 11). The function is roughly parallel to the saturated vapor identity line for alcohols and esters, implying that threshold pungency is evoked at a fixed saturated vapor percentage, regardless of the size or chemical functional group of the stimulating molecule.

Insert Figure 11 about here

In conclusion, there is evidence to support the notion that the action of airborne nonreactive chemicals as either odorants or pungent (mildly irritant) stimuli is mainly due to a physical interaction with susceptible receptor structures. The specific site of action of these stimuli in the cell is not known with certainty but it seems reasonable to assume that a physical interaction with the cell membrane - a lipid bilayer with immersed proteins - is a crucial factor. As the airborne substances become more reactive a sensory

irritation of a chemical nature is superimposed and eventually overcomes the physical effect.

IV Human exposures to airborne contaminants in the field

In real world situations, people are exposed to mixtures of airborne chemicals rather than to single compounds. It is then important to understand how olfaction and the common chemical sense process mixtures of stimuli and how perceived odor and pungency magnitudes of individual compounds compare to the magnitude of the sensations elicited by mixtures of those compounds.

The simplest mixture case is the binary one. An issue of interest is how the sum of the perceived intensities of two chemicals presented alone at a certain concentration compares to the perceived intensity of a mixture in which they are at that same concentration, assuming no chemical interaction between them. Theoretically, the intensity of the mixture could be lower, equal to, or greater than the sum of its components. That is, the mixture could show hypoadditivity, simple additivity, or hyperadditivity, respectively.

Previous studies on the perception of odorant mixtures point out at hypoaddition as the most commonly found phenomena [14, 15, 16, 22, 23, 62, 75, 84, 85, 90, 98, 122]. A few investigations found

simple addition [13, 80, 101], while hyperaddition seems to be uncommon in odor mixtures [80].

Regarding the perception of mixtures of pungent chemicals (the stimuli of the common chemical sense) it was interesting to find, using formaldehyde and ammonia as stimuli, that the degree of additivity of the mixtures was concentration-dependent [45]. That is, at low, medium, and high concentrations of the mixed chemicals, the total perceived intensity of the mixtures showed hypoadditivity, simple additivity, and hyperadditivity, respectively (see Figure 12). The results suggested that the progressively increasing involvement of pungency might have been responsible for the increasing additivity observed. This was confirmed on a subsequent study, in which subjects were asked to estimate the olfactory (odor) and common chemical (pungency) components of those same stimuli [47]. The outcome revealed that odor was always hypoadditive in mixtures whereas pungency was, mainly, additive, and even suggested hyperadditivity (see Figure 13).

Insert Figures 12 and 13 about here

Another factor relevant to the issue of human exposures to airborne contaminants involves the rate of growth of the psychophysical function relating perceived magnitude (of either odor or pungency) with concentration. Odor stimulus-response functions are usually flatter than taste functions, even when compared for the same substances [40], but pungency functions

typically present higher growth rates than those of odor, independently of the scaling procedure employed: category scaling [78] or magnitude estimation [24].

This differences in growth rates can have important practical consequences for odor and irritation control [25]. The steeper the function relating perceived magnitude to concentration, the higher the abatement of sensory intensity that a fixed reduction in ambient concentration (e.g., 100 times) will bring about. If a contaminant or group of contaminants exhibit a very flat stimulus-response function (as seen with some odorants) the perceived intensity might experience little abatement even with a substantial reduction in the airborne concentrations of such chemicals.

Because of the complex rules of additivity in mixtures and the nonlinear and varied nature of psychophysical functions across modalities, it would seem perilous to rely strictly on sensory impressions to gauge the amount of a contaminant or contaminants in the atmosphere.

- Chronic vs. acute exposures

Many substances have been implicated in the production of chronic and/or acute impairment of smell. In a thorough investigation Amoore [8] reviewed many of them, including metallic compounds, dusts, nonmetallic inorganic compounds and organic compounds. He also cited a number of manufacturing and

metallurgical processes responsible for an altered olfactory functioning. Tables 7 to 12 illustrate part of Amoore's compilation.

Insert Tables 7 to 12 about here

Other studies found changes in the smell ability of workers exposed to mercury [58], acrylate and methacrylate vapors [107], and organic solvents [102]. Some of these investigations, however, failed to show an association between chemical exposure and olfactory test scores [107], and still others found the influence of the exposure variable not statistically significant, at least at the exposure levels studied [103]. In a voluntary study at a major chemical manufacturing company it was found that 3 out of about 330 workers (1% of the sample) evidenced marked olfactory dysfunction, and only one was aware of the problem before testing [52].

Human acute exposures are generally the result of accidents. The degree of damage to olfaction depends on the substance itself, its concentration and the time of exposure. Both temporary and permanent effects have been described in acute cases [8]. The already mentioned regenerative capabilities of the olfactory nervous tissue plays an important role in the recovery processes, enhancing its possibilities. Of course in such acute cases, where concentrations are considerably high, the time factor, even in the range of seconds, becomes crucial.

In some instances, people report hypersensitivity, as opposed to hyposensitivity, after acute or chronic exposure to chemicals. In a study of persons reporting symptoms of multiple chemical sensitivity (MCS) - an environmental related disease characterized by hypersensitivity to airborne chemicals and often accompanied by heightened awareness of smells - no evidence of greater olfactory threshold sensitivity was obtained [50].

- Peripheral vs. central toxicity

One issue that arises is whether an airborne contaminant exerts its deleterious action on olfaction or the common chemical sense by directly damaging the receptor structures or by affecting more central structures - e.g., the olfactory bulb or olfactory cortex - via systemic circulation.

These possibilities depend basically on two factors: first, the inherent relative sensitivities of the different structures of the olfactory pathway, and, second, the accessibility of the contaminant to such structures. Given the localization of both odorant and pungent receptor structures in almost direct contact with the external environment, it can be assumed that they will be faced with much higher levels of contaminants - and, hence, would be more likely to be damaged - than the more central components of the pathway. This consideration needs to be counterbalanced - at least in the case of olfaction - with the fact that olfactory receptor

neurons do undergo regeneration, thus providing the periphery with added resistance to deleterious agents.

It is important to consider whether the challenge with airborne contaminants is produced in an acute or chronic way. The former type is more likely to involve high concentrations of the agents -high enough to produce immediate peripheral alterations -, while the latter typically involves relatively low levels of contaminants, raising the possibility of slow buildups on particularly susceptible target structures which could very well be more centrally located. Also, chronic exposures are more likely to affect other organs and systems, in many cases more susceptible of damage than the olfactory or common chemical sensory systems.

- Sensitization vs. tolerance

When assessing the **toxicological** properties of any substance, one of the factors considered involves the study of the way the organism reacts to repetitive challenges with such a substance over time. One possible response might consist in an enhanced reaction when the challenge is repeated. This effect is usually called **sensitization**. The opposite result would be that the response obtained diminishes with each successive identical challenge, in which case it is said that the organism is developing **tolerance** towards the substance in question. In some instances the challenge does not take the form of a repetitive episode but of a continuous one. From the environmental and occupational medicine point of

view tolerance is a particularly undesirable effect since it might render people increasingly unaware of their continuous exposure to potentially harmful substances.

The lapse involved when studying the development of sensitization and tolerance vary to a considerable degree, ranging from hours to months or even years.

Aside from the toxicological point of view, there are comparable concepts employed in the **sensory** realm which generally apply to very short time periods, i.e. in the order of seconds or minutes. **Temporal integration** or **summation** refers to the increased response obtained from continuous or quickly repetitive stimulation of a sensory channel with a constant stimulus. The opposite effect, i.e. a successively diminishing response, is called **adaptation**. Often these two processes act simultaneously and the observed response reflects which one is strongest at a particular time period.

It is well known that the perceived intensity of odors diminishes as a function of time of stimulation [21] except for a short initial phase of integration [49].

Self-adaptation to odors - i.e., adapting the olfactory sense to the same odorant that will be tested - produces a greater abatement of perceived intensity than cross-adaptation - i.e., adapting the sense of smell to a different odorant than the one to be tested [20]. In general, olfactory adaptation exhibits unpredictable specificity and

cross-adaptation is often asymmetric, that is, odorant A may have a stronger effect on odorant B (diminishing its perceived intensity and raising its threshold) than vice versa [81].

The human response to nasal stimulation with pungent chemicals shows a phenomenon of temporal integration rather than adaptation, at least over the first few seconds of stimulation [42] (see Figure 14). Temporal integration of pungency - irritation - can continue even for minutes: Figure 15 illustrates the time course of perceived irritation caused by exposure to 1 ppm formaldehyde over a 90 min period, showing first an increase in irritation with time (temporal integration), and then a decrease (adaptation). In general, common chemical sensations (pungency) show a longer onset latency but they last longer and are more resistant to adaptation than olfactory sensations [24, 27, 29]. These results refer, of course, to very short term exposures, characteristic of sensory experiments. Over longer periods of exposure it is possible to develop tolerance to pungency or irritation from airborne chemicals. One such example is the relative insensitivity that smokers develop to the pungency evoked by CO_2 [41, 56] as will be discussed in section VI.

Insert Figures 14 and 15 about here

V Measurement of chemosensory changes in exposed populations

- Instrumental and psychophysical procedures of measurement and their limitations

Measurement of olfactory functioning

Traditionally, testing of the olfactory sense in a clinical setting has been characterized by its crudeness and lack of quantitation and standardization. An early attempt in the 1930s used the so called blast injection technique to measure odor thresholds and this technique, known as the Elsberg method, was recommended for a time in some neurology manuals [57]. Later on, indications were found that the procedure might have measured air pressure thresholds rather than olfactory thresholds [74].

Subsequent attempts continued to use threshold measurements as an index of functioning [9, 70]. As pointed out by Cain et al. [30], given our lack of knowledge of how alterations in threshold reflect in suprathreshold sensations (the type we experience most commonly in everyday life), threshold performance alone should not be the only clinical index of olfactory functioning. Accordingly, these authors developed a composite test comprising a threshold and a suprathreshold (odor identification) component [30]. The test was later known as the Connecticut Chemosensory Clinical Research Center (CCCRC) test [28, 31].

The threshold part of this test employs a series of aqueous dilutions of 1-butanol, starting at 4 % v/v (approximately 3000 ppm

in the vapor phase), named dilution step 0, and where successive dilutions differ by a factor of 3 - i.e. dilution step 1 = 1.33 % ; dilution step 2 = 0.44 %, etc. The full series includes steps 0 to 11 (4 % to 2.3 x 10^{-5} % v/v) corresponding to vapor phase concentrations ranging from 3000 ppm to 46 ppb. Sixty ml of these solutions are presented for smelling in 250 ml-capacity squeezable plastic bottles with pop-out spouts that fit into the nostril, thus allowing for each nostril to be tested separately. In each trial subjects have to choose the stronger of two stimuli, one stimulus being the blank - water - and the other a butanol dilution step. Testing begins with the lowest concentration. An incorrect choice leads to the presentation of the next higher concentration paired with a blank. If the patient chooses correctly, the same concentration and a blank (both from a duplicate set) are again presented until an error is made or five correct choices in a row are made, in which case that concentration is taken as the threshold.

The odor identification component of the CCCRC test uses environmentally realistic odorants, including an item that appeals to the common chemical sense (pungency), thus roughly assessing also trigeminal nerve function. This part of the test is a modification of a previously devised test [32] which employs highly identifiable items chosen from previous research [26]. Stimulus presentation technique for this component of the CCCRC test also allows the separate evaluation of each nostril. In this case patients seek to identify each odor presented with the help of a list containing 16 terms: 8 describe actual items in the test and 8 describe other

common items. The patient is also allowed to respond "no sensation" or "I smelled something but I don't know what it is."

Another test of olfactory function is the University of Pennsylvania Smell Identification Test (UPSIT) [51, 53, 55]. This test consists of four booklets, each containing 10 "scratch & sniff" odorants. The stimuli are released by scratching the strips with a pencil tip. Above each odorant strip is a multiple-choice question with four response alternatives for each item. Upon release of each stimulus the subject is forced to choose one of the four alternatives, even if no smell is perceived. The number of correct responses is computed and compared with previously obtained data from normal subjects and patients with various types of diseases.

It has also been observed that both the CCCRC and the UPSIT tests render highly comparable results, though they might convey diagnostically useful differences worthwhile of future studies [35].

Measurement of common chemical sense functioning

The olfactory tests just mentioned only marginally touch the issue of the perception of airborne pungent substances through the free nerve endings of the trigeminal nerve in the mucosae of the face.

One of the major difficulties in this realm stems from the absence of chemicals that selectively stimulate common chemical sensitivity and not olfaction and vice versa. Nevertheless, as mentioned at the

beginning of this chapter, the particular choice of CO_2 as the pungent stimulus allows evocation of both oral and nasal pungency [41, 46, 48, 56, 65, 111] with a relatively innocuous substance that, at the same time, is almost odorless [34].

When the concentration of a pungent stimulus entering the nose reaches a certain level, a non-systemic, reflexive interruption of inhalation eventually occurs in all persons [41, 42, 56, 65] (see Figure 16). We believe that this reflex could become an objective indicator of functional status of the nasal common chemical sense.

Insert Figure 16 about here

In three studies, the assessment of this reflex transitory apnea has yielded excellent quantitative agreement with psychophysical data. In the first, the threshold for the reflex exhibited the same degree of bilateral integration as seen psychophysically [65]. In the second, cigarette smokers exhibited a higher threshold to the reflex than did nonsmokers, a result that quantitatively agreed with psychophysical judgements of perceived pungency in the two groups [41]. In the third, using another pungent stimulus: ammonia, the threshold displayed virtually the same degree of temporal summation as that seen psychophysically [42], that is both the reflex and a fixed degree of perceived pungency can be achieved at a lower concentration of the irritant if the inhalation time of the stimulus is proportionally increased.

- Effect of demographic variables (age, sex, smoking) on sensitivity to airborne contaminants

Smoking and gender

Previous investigations addressed the question of whether smoking or gender would affect olfactory sensitivity. They ended up with conflicting results since some of them found differences and others not [61, 76, 79, 100, 118]. A very recent study of 638 subjects with the UPSIT test found a dose-related impairment of odor identification with smoking in both current and previous smokers [64]. The results of this investigation suggest that: 1) smoking causes long term but reversible adverse effects on the ability to smell, and 2) the failure of some studies to demonstrate smoking effects may be caused by the inclusion of persons with a history of smoking in the nonsmoking groups.

Also, a number of studies were carried out to explore the influence of these same demographic variables on common chemical sensitivity. Measurements of the above mentioned pungency-induced reflex interruption of inhalation have indicated that smokers are less sensitive, i.e., present higher thresholds for the reflex, than nonsmokers [56]. Even immediately after short periods of smoking (6-10 min) it was possible to detect a further impairment in the smoker's sensitivity to the production of this transitory apnea [41]. It then seems that, on top of the chronic reduction of

pungency sensitivity with smoking, there is also an acute desensitization immediately after smoking.

A question of interest concerned whether the observed group differences in sensitivity represent differences in the magnitude of the sensation experienced, rather than differences in the efferent side of the reflex loop. From results obtained in smokers and nonsmokers it was noted that the threshold for transitory apnea occurred at a criterion level of perceived magnitude and that the psychophysical function for pungency differed between both groups by a roughly constant factor across concentrations [41]. This could imply that the impairment in pungency perception seen in smokers arises from peripheral, even pre-neural factors, such as mucus thickness and lack of ciliary motility, which might play an obstructive role, impeding the transfer of molecules of inhaled irritants from the air to the free nerve endings.

Interestingly, it was also found that females are more sensitive than males towards this reflex, regardless of whether it is evoked unilaterally or bilaterally [56, 65]. The difference between genders started to emerge even within the smoker and nonsmoker groups [56].

In subsequent experiments it was shown that females not only produced the reflex apnea at lower concentrations than males but they also produced steeper stimulus-response functions for nasally-evoked CO_2 pungency. Furthermore, females were experiencing

more nasal pungency from the same range of CO_2 concentrations than their male counterparts, as gauged by a magnitude matching procedure using sucrose's sweetness as the reference modality [48] (see Figure 17). No differences of either kind - steepness of psychophysical function or relative perceived pungency - were observed when CO_2 was employed to produce buccal, rather than nasal, pungency in males and females.

Insert Figure 17 about here

Age

Studies that addressed the issue of how olfaction is affected by aging invariably have concluded that aging takes a toll [37, 121]. The elderly have higher thresholds [106, 112, 113, 118], perceive suprathreshold odors as being weaker [109, 110, 112, 113, 114], discriminate, recognize and identify common odors less well [54, 92, 104, 105], and remember episodic presentations of odors poorly [33, 92]. A couple of investigations have also shown that common chemical sensitivity is diminished in the elderly [111, 114].

The available information indicates that the process of deterioration sets in relatively early in life, progresses gradually, and that males lose sensitivity at a greater rate than females [31, 54, 93, 118].

In general, it seems that the blunting of olfactory sensitivity with age is, to a first approximation, uniform for all odor qualities [37], though some odorants, for which people's ability to smell them is thought to be genetically determined [10, 120], may behave differently [121].

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Tables

TABLE 1. *Main chronic nonneoplastic lesions of the nasal respiratory mucosa in experimental animals*

Simple, papillary, and nodular epithelial hyperplasia with or without atypia
Stratified squamous metaplasia with or without keratinization of the epithelium (reversible/irreversible)
Excessive hyperkeratosis (with or without inflammatory exudate) leading to obstruction of the nose
Glandular hyperplasia of submucosal glands (adenomatosis)
Rhinitis/infiltration of the mucosa and submucosa with inflammatory cells
Rarefaction of turbinate bones

From Feron et al., ref. 60.

TABLE 2. *Main types of tumors of the nasal respiratory mucosa in experimental animals*

Papilloma
Exophytic
Endophytic (inverted)
Adenoma (of submucosal glands)
Polypoid adenoma (exophytic)
Squamous cell carcinoma
Adenocarinoma
Adenosquamous carcinoma
Anaplastic carcinoma

From Feron et al., ref. 60.

TABLE 3. *Main chronic nonneoplastic lesions of the nasal olfactory mucosa in experimental animals*

Atrophy of sensory cells
Atrophy of olfactory epithelium
Replacement of olfactory epithelium by respiratorylike epithelium
Replacement of olfactory epithelium by goblet or ciliated cells
Replacement of olfactory epithelium by keratinized squamous epithelium
Accumulations of sensory cells in the submucosa
Karyo- and cytomegaly of epithelial cells of Bowman's glands
Reduced number or loss of Bowman's glands
Cystlike structures in the submucosa
Rhinitis or necrotizing rhinitis
Infiltration of the mucosa and submucosa with inflammatory cells
Thickened submucosa due to edema and increased amount of loosely arranged fibrous tissue
Loss of nerve bundles in the submucosa

From Feron et al., ref. 60.

TABLE 4. *Main types of tumors of the nasal olfactory mucosa in experimental animals*

Adenocarcinoma
From basal cells
From glands of Bowman
With sustentacular cell differentiation
With neuroendocrine cell differentiation
Esthesioneuroepithelioma, from sensory cells
Neuroepithelioma

From Feron et al., ref. 60.

TABLE 5. *Mucociliary apparatus: potential mechanisms proposed for defective mucociliary function in airway diseases or following exposure to air pollutants*

Structural component	Proposed toxic modification	Example: known or postulated as mechanism of action
1. Osmiophilic membrane	Altered surface tension	NF[a]
2. Epiphase	a. Altered viscoelasticity	Chronic bronchitis; cigarette smoke; formaldehyde
	b. Excessive quantity	Chronic bronchitis; cystic fibrosis; asthma
	c. Tethering to goblet cells	Dehydration
3. Hypophase	a. Altered viscoelasticity	NF
	b. Increased amount	Postulated
	c. Altered composition	Cystic fibrosis
	d. Altered pH	Sulfuric acid mist
4. Cilia	a. Decreased or no activity or loss of cilia	Numerous gaseous irritants; cigarette smoke
	b. Reduced beat frequency	Cadmium salts; acetaldehyde
	c. Reduced amplitude of beat	Dimethylamine
	d. Incoordinated beating	Cigarette smoke
	e. Reversed direction of beat	Cigarette smoke, dimethylamine
5. Microvilli	Impairment of function	NF
6. Cell junctions	Leakage of macromolecules and/or small ions	Cigarette smoke; antigen challenge; diethyl ether
7. Epithelial cells	a. Defective ion transport	Cystic fibrosis; physical trauma
	b. Altered intracellular pH	Ammonium and sulfate ions
	c. Defective energy metabolism	Cadmium
	d. Cell death	Many irritants at high enough concentration
8. Blood vessels	Increased permeability	Allergy
9. Mucoserous glands	Reduced, excessive, or altered secretions	NF
10. Nerves	a. Increased goblet cell or glandular secretions	Pharmacologic agents
	b. Modified ciliary activity	NF for mammalian system

From Morgan et al., ref. 89.

[a]NF, no example was found in the available literature.

TABLE 6. *The RD_{50} values, 1983 TLV-TWA values, and TLV-TWA values predicted on the basis of 0.03 RD_{50} for 40 industrial chemicals*

Chemical no. in Fig. 5	Chemical name	RD_{50} (ppm)	1983 TLV-TWA (ppm)	0.03 RD_{50} (ppm)
1	2, 4-Toluene diisocyanate	0.2	0.005	0.006
2	Chlorobenzylidene malononitrile	0.52	0.05	0.016
3	Chloracetophenone	0.96	0.05	0.029
4	Acrolein	1.68	0.1	0.05
5	Formaldehyde	3.13	2.0	0.10
6	Benzoquinone	5.0	0.1	0.15
7	Chloropicrin	7.98	0.1	0.24
8	Chlorine	9.34	1	0.28
9	Benzylchloride	17.0	1	0.51
10	Isophorone	27.8	5	0.83
11	Sulfur dioxide	117	2	3.5
12	Acetic acid	163	10	4.9
13	Phenol	166	5	5.0
14	*o*-Dichlorobenzene	182	50	5.5
15	Ammonia	303	25	9.1
16	Hydrogen chloride	309	5	9.3
17	Ethyl acrylate	315	5	9.5
18	*p*-tert-Butyltoluene	360	10	11
19	Dimethylamine	511	10	15
20	Ethyl acetate	614	400	18
21	Epichlorohydrin	687	2	20
22	Cyclohexanone	756	25	23
23	Styrene	980	50	29
24	Chlorobenzene	1,054	75	32
25	*o*-Xylene	1,467	100	44
26	Amyl acetate	1,531	100	46
27	Isopropylbenzene (Cumene)	2,490	50	75
28	2-Butoxyethanol	2,825	25	85
29	Methylisobutyl ketone	3,195	50	96
30	Ethylbenzene	4,060	100	122
31	Isoamyl alcohol	4,452	100	134
32	*n*-Butyl alcohol	4,785	50	143
33	Acetaldehyde	4,946	100	148
34	Toluene	5,300	100	159
35	Methyl ethylketone	9,000	200	270
36	*n*-Propyl alcohol	12,704	200	381
37	Isopropyl alcohol	17,693	400	531
38	Ethyl alcohol	27,314	1,000	819
39	Methyl alcohol	41,514	200	1,245
40	Acetone	77,516	750	2,345

From Alarie and Luo, ref. 7.

RD_{50}, concentration of irritant to cause 50% decrease in respiratory rate; TLV-TWA, threshold limit value-time weighted average.

TABLE 7. *Metallurgical processes considered responsible, on chronic exposure, for permanent hyposmia in humans*

Substance	Exposure time (years)	Olfactometric method	Incidence of hyposmia: Frequency %	Incidence of hyposmia: Rating[a] (steps)	Assessment
Chromium	1.5	Elsberg	17	(−0.7)	Below average
Chromium plating	4	Recognition	Cohort		Low normal
Lead	8	Elsberg	33	(−0.6)[b]	Below average
Lead (severe intoxication)		Elsberg	Cohort	−1.2	Below average
Lead (severe intoxication)		Elsberg	Cohort	−1.3	Below average
Magnet production[c]	10	Recognition	10 cases		Hyposmia
Mercury (chronic intoxication)	29	Elsberg	55	−3.6	Low normal
Nickel plating	4	Recognition	Cohort		Low normal
Nickel refining (electrolytic)	> 5	Recognition	33		Anosmia
Silver plating	6	Recognition	Cohort		Below average
Steel production	4	Elsberg	6	< −3.3	Low normal
Zinc production	> 5	Elsberg	3	< −2.7	Low normal

From Amoore, ref. 8.
[a]Values reflect olfactory deficit, measured according to a pyridine binary dilution step scale.
[b]Just one worker was affected, and he had a unilateral hyposmia.
[c]Iron, aluminum, nickel, cobalt, and chromium powders.

TABLE 8. *Metallic compounds considered responsible, on chronic exposure, for permanent hyposmia in humans*

Substances	Exposure: Concentration (mg/m³)	Exposure: Time (years)	Olfactometric method	Incidence of hyposmia: Frequency (%)	Incidence of hyposmia: Rating[a] (steps)	Assessment
Cadmium compounds	—	—	Elsberg	13	—	Anosmia
Cadmium compounds[b]	1.3	7	Elsberg	66	—	Hyposmia[c]
Cadmium oxide	—	3	Recognition	1 case	—	Anosmia
Cadmium oxide / Nickel hydroxide	9 / 80	20	Symptom	44	—	Anosmia
Cadmium oxide / Nickel hydroxide	0.5[e] / 0.01	15	Proetz	27	< −7.6	Hyposmia
Chromate salts	—	18	T&T	27	< −18	Anosmia
Zinc chromate	10	10	Roseburg	30	~ −7	Hyposmia[f]

From Amoore, ref. 8.
[a]Values reflect the olfactory deficit, measured according to a pyridine binary dilution step scale.
[b]Oxide, sulfate, carbonate, nitrate, sulfide, selenide, stearate.
[c]The hyposmia was ameliorated by giving caffeine.
[d]Before dust control.
[e]After installation of industrial hygiene equipment.
[f]A follow-up study on 11 of the same workers 4 years later (after reducing the chrome dust exposure in the factory) showed no recovery of olfactory performance

TABLE 9. *Dusts considered responsible, on chronic exposure, for permanent hyposmia in humans*

Substances	Exposure time (years)	Olfactometric method	Incidence of hyposmia		
			Frequency (%)	Rating[a] (steps)	Assessment
Cement	—	Proetz	2	—	Hyposmia
Chemicals	6	Proetz	8	< −6.6	Hyposmia
Hardwoods	—	Symptom	5	—	Anosmia
Hardwoods	—	Symptom	—	—	Anosmia
Lime	—	Proetz	6	—	Hyposmia[b]
Printing	—	Naus	24	−3.0	Low normal
Silicosis (first stage)[c]	—	Elsberg	Cohort	−1.2	Below average

From Ammore, ref. 8.

[a]Values reflect the olfactory deficit, measured according to a pyridine binary dilution step scale.

[b]Damage to the olfactory epithelium, sensory cells, and bulbar fibers was observed in rats exposed 2 months in the dustiest locations in the factory.

[c]First-, second-, and third-stage silicosis cohorts all showed about the same olfactory deficit.

TABLE 10. *Nonmetallic inorganic compounds considered responsible, on chronic exposure, for permanent hyposmia in humans*

Substance	Exposure		Olfactometric method	Incidence of hyposmia		
	Concentration (ppm)	Time (years)		Frequency (%)	Rating[a] (steps)	Assessment
Carbon disulfide	—	15	Elsberg	22	−3.4	Low normal
Carbon disulfide (average intoxication)	—	—	Elsberg	Cohort	−2.0[b]	Low normal
Carbon disulfide (intoxication)	62	20	Elsberg	14		Hyposmia
Carbon monoxide	—	13	Recognition	1 case	—	Anosmia
Carbon monoxide (intoxication)[c]	> 100		Elsberg	6	—	Ansomia
Chlorine	—	3	Proetz	70	< −6.6	Hyposmia
Hydrazine	—	—	Elsberg	Cohort	−0.8	Below average
Nitrogen dioxide (NO_x)	3	5	Elsberg	Cohort	−0.7	Below average
Ammonia	30					
Nitrogen dioxide (NO_x)	—	8	Proetz	60	< −6.6	Hyposmia
Sulfur dioxide (SO_x)						
Sulfur dioxide	90	4	Symptoms	14	—	Hyposmia
Sulfur dioxide	155	20	Elsberg	Cohort	−3.4	Low normal
Sulfur dioxide	80	32	T&T	Cohort	−4.4	Hyposmia
Ammonia[d]						
Sulfur dioxide (SO_x)	—	> 5	Elsberg	Cohort	−1.2	Below average
Nitrogen dioxide (NO_x)						
Fluorides (HF?)						

From Amoore, ref. 8.

[a]Values reflect the olfactory deficit, measured according to a pyridine binary dilution-step scale.

[b]The hyposmia could be partially or completely reversed, for 1 or 2 h, by injections of caffeine or eserine.

[c]Includes both acute and chronic intoxications.

[d]Workers exposed to ammonia alone showed no significant olfactory deficit.

TABLE 11. *Organic compounds considered responsible, on chronic exposure, for permanent hyposmia in humans*

Substances	Exposure		Olfactometric method	Incidence of hyposmia		
	Concentration (ppm)	Time (years)		Frequency (%)	Rating[a] (steps)	Assessment
Acetone	—	8	Recognition	1 case	—	Hyposmia
Acetophenone	—	6	Elsberg	12	(< −2.3)	Low normal
Benzene	—	10	Elsberg	Cohort	−0.8	Below average
Benzine	400	5	Proetz	37	−6	Hyposmia
Benzine Ethyl acetate Butyl acetate	60	8	Elsberg	30	< −3.1	Low normal
Chloromethanes[b]	—	—	Elsberg	44	−2.7	Low normal
Menthol	—	—	Recognition	Cohort	—	Hyposmia
Menthol	—	45	Symptom	1 case	—	Hyposmia
Pentachlorophenol	—	—	Symptom	1 case	—	Anosmia[c]
Trichloroethylene	380	10	Naus	Cohort	3.1[d]	Low normal
Trichloroethylene (intermittent abuse)	Sat. vap.	9	Symptom	1 case	—	Complete anosmia

From Amoore, ref. 8.

[a]Values reflect the olfactory deficit, measured according to a pyridine binary dilution step scale.

[b]CH_3Cl, CH_2Cl_2, $CHCl_3$, CCl_4.

[c]May have been due to upper respiratory tract infection, not occupational exposure.

[d]Tested at beginning of shift, i.e., a permanent hyposmia. When tested at the end of the shift, an additional −2.1 steps of temporary hyposmia were demonstrated.

TABLE 12. *Manufacturing processes considered responsible, on chronic exposure, for permanent hyposmia in humans*

Substance	Exposure time (years)	Olfactometric method	Incidence of hyposmia		
			Frequency (%)	Rating[a] (steps)	Assessment
Acids (organic and inorganic)	7	Proetz	5	< −6.6	Hyposmia
Asphalt (oxidized)	6	Elsberg	18	< −2.3	Low normal
Cutting oils (machining)	—	Elsberg	Cohort	−0.8	Below average
Fragrances	4	Recognition	50	—	Below average
Paint (lead)	—	Naus	56	−2.9	Low normal
Paprika	14	Elsberg	4	—	Hyposmia
"Pavinol" (sewing)[b]	—	Elsberg	55	< −2.3	Low normal
Spices	11	Naus	Cohort	−1.0[c]	Below average
Tobacco	12	Elsberg	1	—	Hyposmia
Varnishes	10	Recognition	78	—	Low normal
Varnishes	5	Elsberg	1	—	Hyposmia
Wastewater (refinery)	7	Elsberg	18	< −2.3	Low normal

From Amoore, ref. 8.

[a]Values reflect the olfactory deficit, measured according to a pyridine binary dilution step scale.

[b]A synthetic leather. The material contains a slightly volatile plasticizer, dibutyl phthalate, which may be responsible for the hyposmic effect.

[c]Tested at the beginning of the shift, i.e., a permanent hyposmia. When tested at the end of the shift, an additional −1.6 steps of temporary hyposmia were demonstrated.

Figure Legends

Figure 1. Lateral wall of the nasal cavity with the olfactory region (hatched area). (A) Skin in the nostril. (B) Squamous epithelium without microvilli. (C) Transitional epithelium with short microvilli of varying length, but uniform within the single cell. (D) Pseudostratified columnar epithelium with few ciliated cells. (E) Pseudostratified columnar epithelium with many ciliated cells. From Mygind et al. [94].

Figure 2. Diagram of the structural elements found in the olfactory mucosa (from Hornung and Mozell [72]).

Figure 3. Diagrammatic representation of the nasal respiratory epithelium to show the main components. The thickness of the mucus and the epithelium vary considerably throughout the nose, as do the relative proportions of the different cell types. The nerves present in the subepithelial region often extend through the basement membrane, and lie both beneath and between the epithelial cells. Key: OM, osmiophilic membrane; EP, epiphase; HY, hypophase; CI, cilia; MV, microvilli; CJ, cell junction; CC, ciliated cell; NCC, nonciliated cell; GC, globet cell; NE, nerve; GL, gland; BV, blood vessel; ECS, extracellular space; BM, basement membrane. From Morgan et al. [89].

Figure 4. Recording of tidal volume and respiratory rate from a mouse in a body plethysmograph during room air breathing (top)

and during inhalation of a sensory irritant (bottom). Inspiration is upward; note the characteristic pause during expiration. From Alarie and Luo [7].

Figure 5. Linear least-squares regression analysis for 40 chemicals, plotting log of $0.03RD_{50}$ as the proposed TLV-TWA versus the log of the 1983 TLV-TWA value for each chemical. Regression equation: Y = 0.302 + 0.81 X. Standard deviation of Y about the regression line = 0.48, r = 0.92. The correlation line, slope = 1, is given by the dashed line. Identification of the chemical for each number can be obtained from Table 6. From Alarie and Luo [7].

Figure 6. A model for physical and chemical interaction of sensory irritants with a receptor protein located in a lipid bilayer. A protein, left-side solid line, containing a disulfide bond which can be cleaved by disulfide splitting agents such as sulfur dioxide. This site could also serve for adsorption of the benzene ring of alkylbenzenes, their alkyl chains projecting further down in the lipid layer as shown. A nucleophilic group, near the disulfide bridge, is for the action of alkylating agents, such as bromoacetylcholine as shown, and for potent sensory irritants having high reactivity toward such a group. Molecules containing a hydrophilic group, such as the aliphatic alcohols shown, would be oriented parallel to the lipophilic chain of the phospholipid layer. The orienting effect thereby obtained would allow different hydrophilic groups with different alkyl chains to physically disturb

the receptor protein in a manner similar to alkylbenzenes. From Nielsen and Alarie [96].

Figure 7. Odor thresholds measured in normals (empty symbols) and pungency thresholds measured in anosmics (filled symbols) for a homologous series of aliphatic alcohols from methanol to 1-octanol, represented by the numbers 1 to 8, respectively (from Cometto-Muñiz and Cain [43]).

Figure 8. Same odor (empty symbols) and pungency (filled symbols) thresholds as in Figure 7 but expressed as thermodynamic activity. Activity was calculated as the ratio between vapor concentration at threshold odor or pungency over saturated vapor concentration, multiplied by 100. From Cometto-Muñiz and Cain [43].

Figure 9. Odor thresholds measured in normals (empty symbols) and pungency thresholds measured in anosmics (filled symbols) for two homologous series: a) alcohols (circles), from methanol to 1-octanol and b) esters - acetates - (squares), from methyl acetate to octyl acetate. The abscissa indicates the number of carbon atoms in the variable chain. From Cometto-Muñiz and Cain [44].

Figure 10. Same odor (empty symbols) and pungency (filled symbols) thresholds for homologous alcohols (circles) and acetates (squares) as in Figure 9 but expressed as thermodynamic activity. Activity was calculated as the ratio between vapor concentration at

threshold odor or pungency over saturated vapor concentration, multiplied by 100. From Cometto-Muñiz and Cain [44].

Figure 11. Average odor (empty circles and squares) and pungency (filled circles and squares) thresholds (obtained from normals and anosmics, respectively) as a function of saturated vapor concentration for the aliphatic alcohols and acetate esters homologous series. Data depicted from methanol and methyl acetate, on the upper right of each series, to 1-octanol and octyl acetate, on the lower left. From Cometto-Muñiz and Cain [44].

Figure 12. Total nasal perceived intensity for each of the 16 formaldehyde and ammonia binary mixtures as a function of the sum of the perceived intensities of their components, presented at the same concentration as in the mixtures but alone. The dotted line represents the identity line (slope = 1.00). It can be seen that at low, medium, and high intensities the perceived intensity of the mixtures depict hypoadditivity, simple additivity, and hyperadditivity, respectively - i.e., the experimental points fall below, around, and above the identity line, respectively. From Cometto-Muñiz et al. [45].

Figure 13. Relationship between the perceived intensity of each of the 16 formaldehyde-ammonia binary mixtures for (A) total nasal intensity, (B) odor, and (C) pungency; and the sum of the perceived intensities of the components of each mixture for that same attribute. Even when the mixtures are the same, the data belong to a

different experiment than that shown in Figure 12. Note that odors are always hypoadditive - i.e., points fall below the identity line - while pungency is mainly additive - i.e., points lie around the identity line - and even suggest hyperadditivity at high enough levels - i.e., points lie above the identity line. From Cometto-Muñiz and Hernández [47].

Figure 14. Perceived magnitude as a function of duration of inhalation for a benign odorant: isoamyl butyrate, and a pungent one: ammonia. The parameter in both graphs is concentration. From top to bottom, concentration equalled 71.9, 24.8, and 9.6 ppm, respectively, for isoamyl butyrate; and 434, 225, 99, and 47 ppm, respectively, for ammonia. Note that only the perceived magnitude of the pungent odorant increases significantly with inhalation time - thus showing temporal integration or summation. From Cometto-Muñiz and Cain [42].

Figure 15. Exponential equation of the form $Y = (a - be^{-ct}) \cdot e^{-gt}$, where Y=perceived increasing and then decreasing magnitude, t=time, and a, b, c, and g are constants, fitted to irritation caused by exposure to 1 ppm formaldehyde (from Cain et al. [36]).

Figure 16. Breathing patterns detected by changes in temperature of a nasal thermocouple before, during, and after presentation of CO_2 at a concentration sufficient to elicit reflex, transitory apnea. The upper tracing shows a typical response whereas the lower

tracing shows a particularly pronounced disruption of inhalation. From Cometto-Muñiz and Cain [41].

Figure 17. Left part. Psychophysical functions obtained by magnitude matching of CO_2 nasal pungency (circles) and sucrose sweetness (triangles) in males (filled symbols) and females (empty symbols). Comparison between genders is not appropriate without normalization since each subject was allowed to assign any number deemed appropriate to the first stimulus of the session. Right part. This side depicts the same functions as in the left for males. The functions for females were multiplied by a factor that brought into coincidence the judgments of sweetness intensity from females with those of males. This normalization was performed under the assumption of no intensity differences in sweetness perception between genders, and allows a meaningful comparison of pungency intensity along the ordinate. From Cometto-Muñiz and Noriega [48].

FIGURE 1

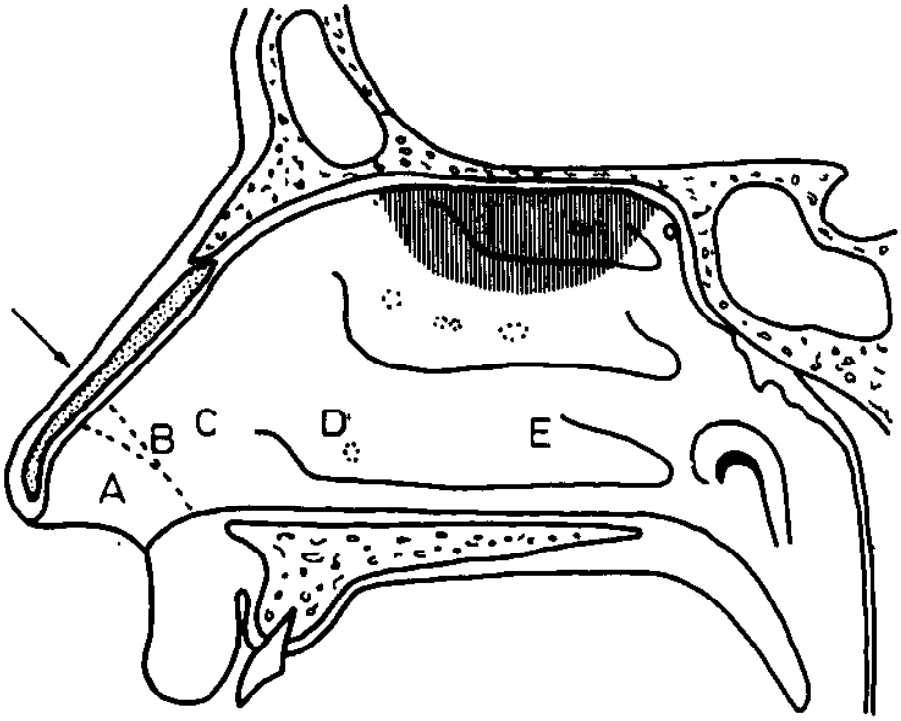


FIGURE 2

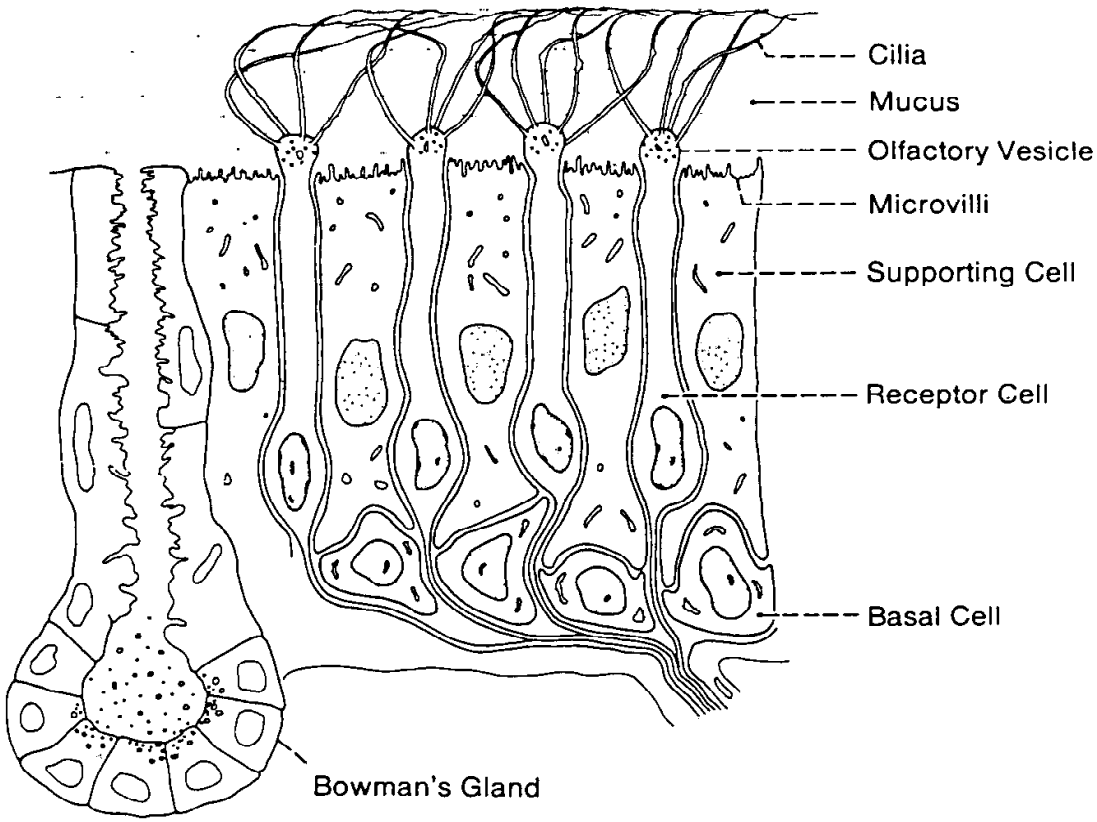


FIGURE 3

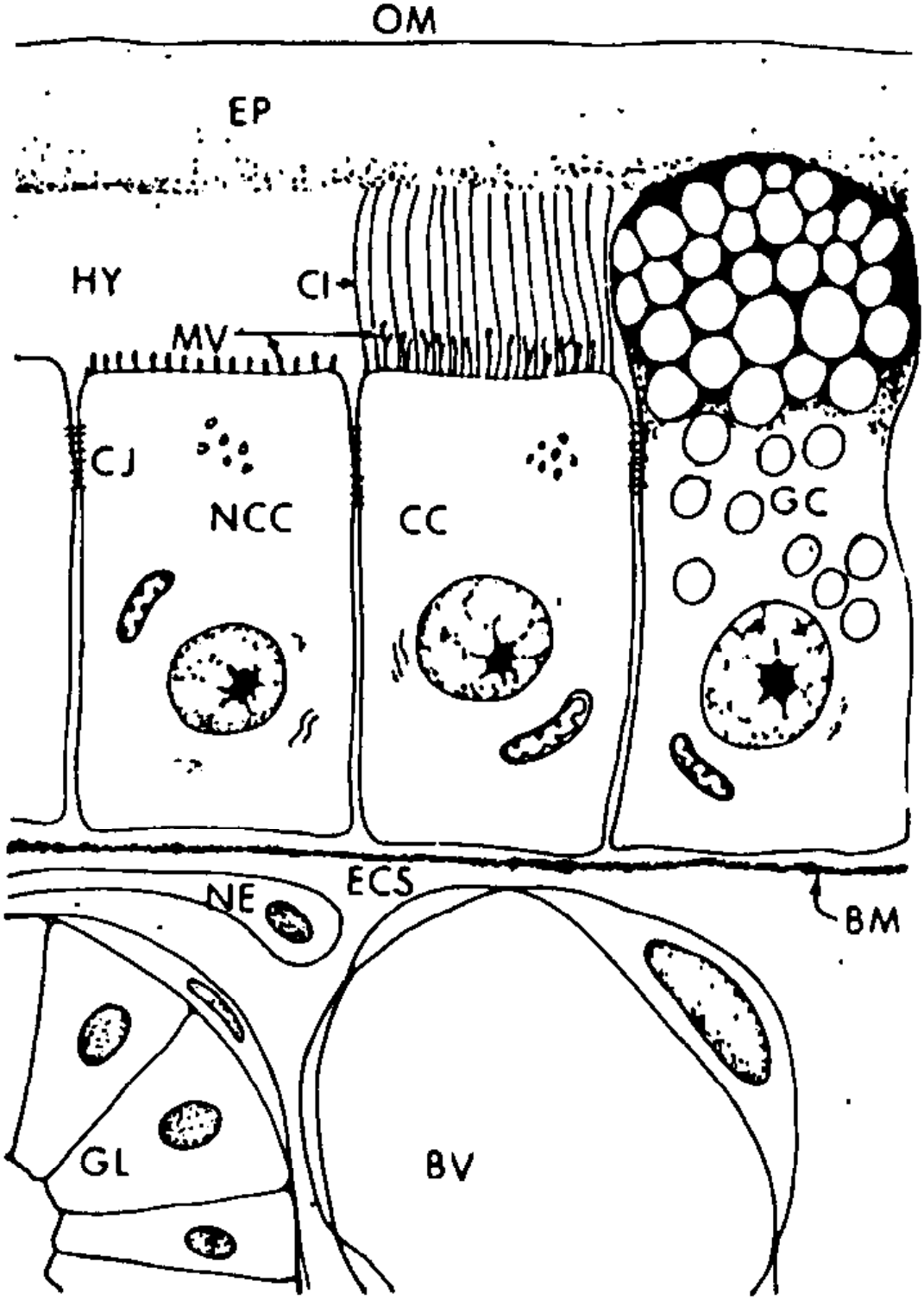


FIGURE 4

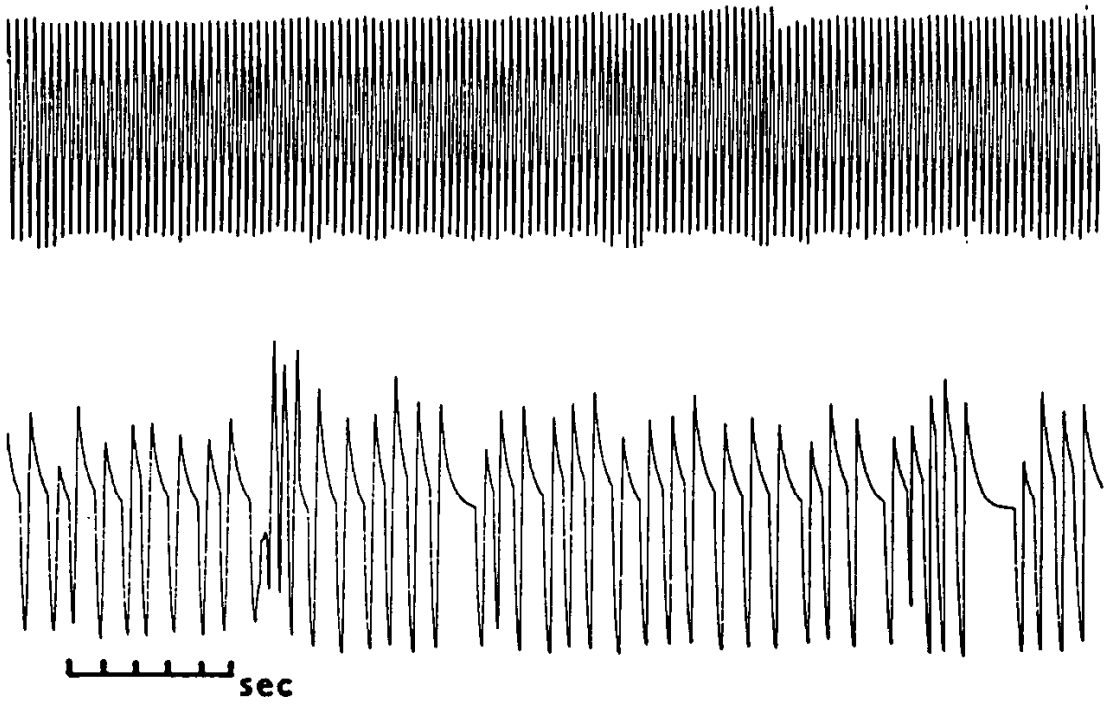


FIGURE 5

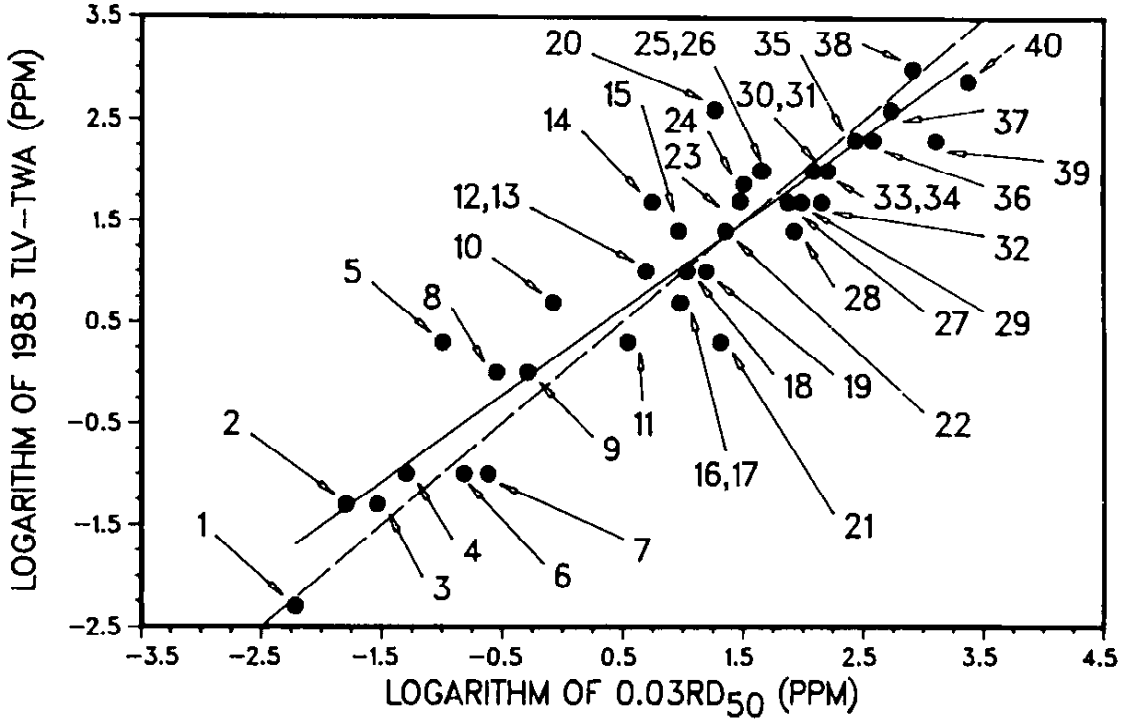


FIGURE 6

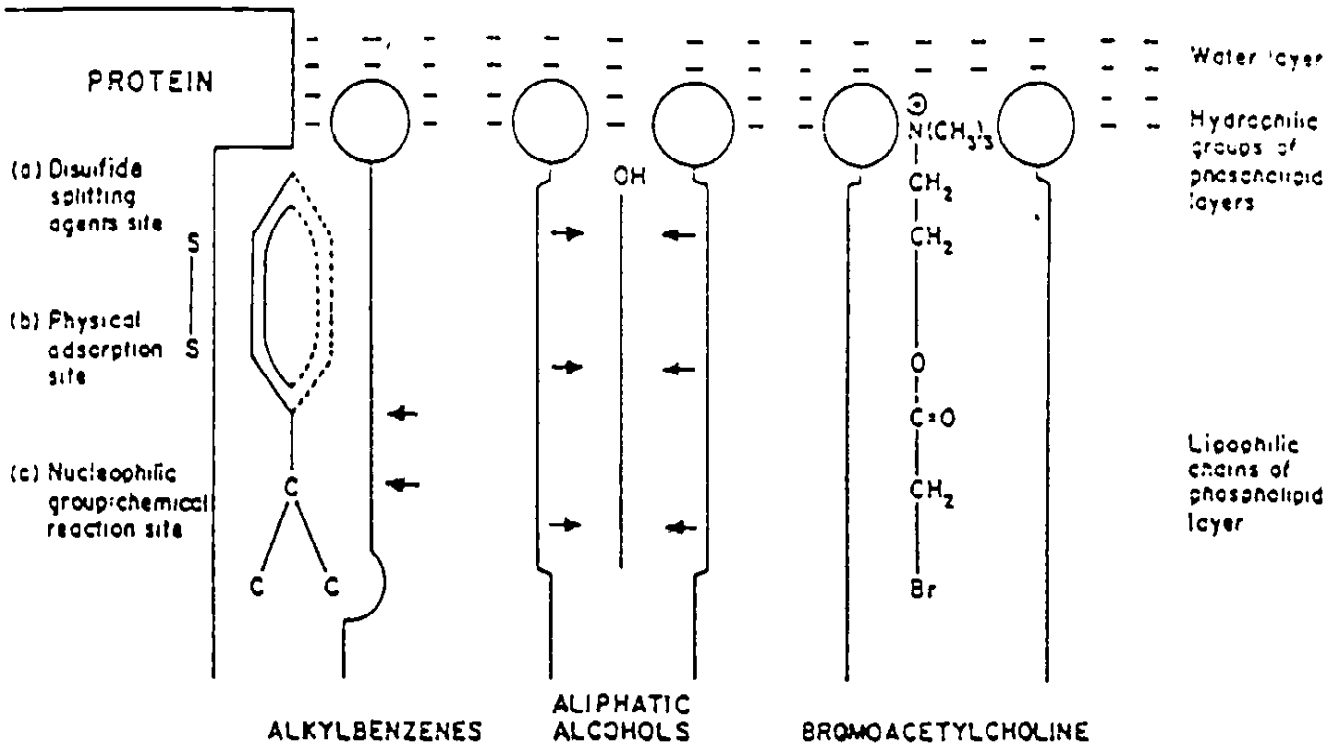


FIGURE 7

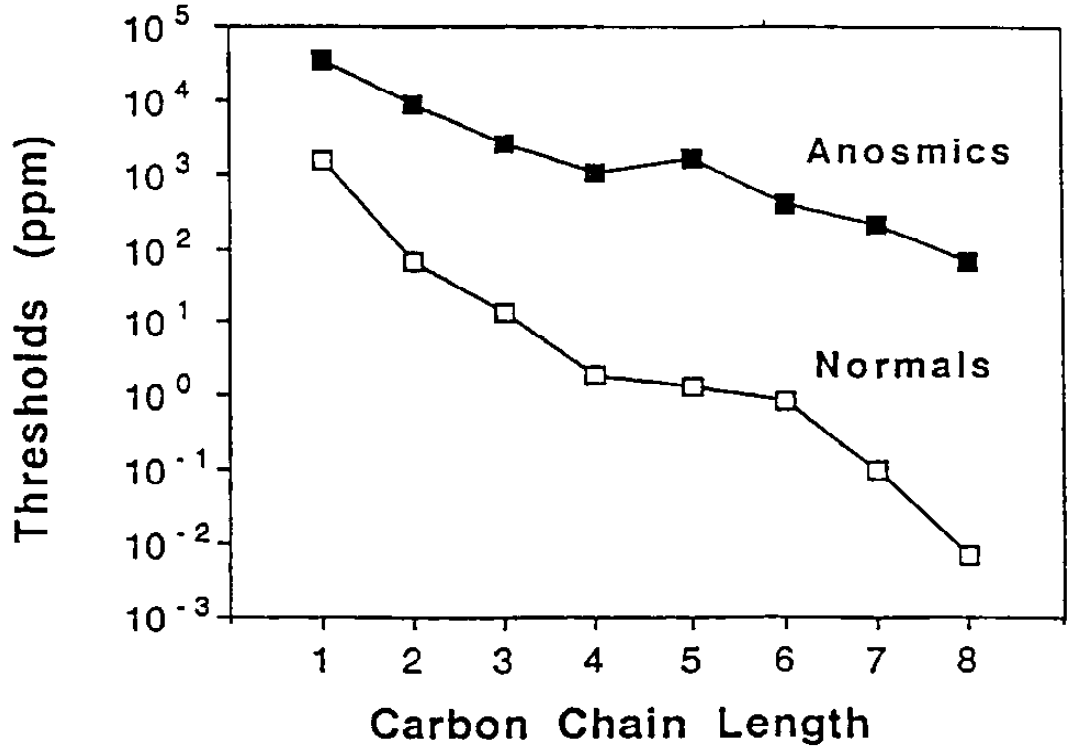


FIGURE 8

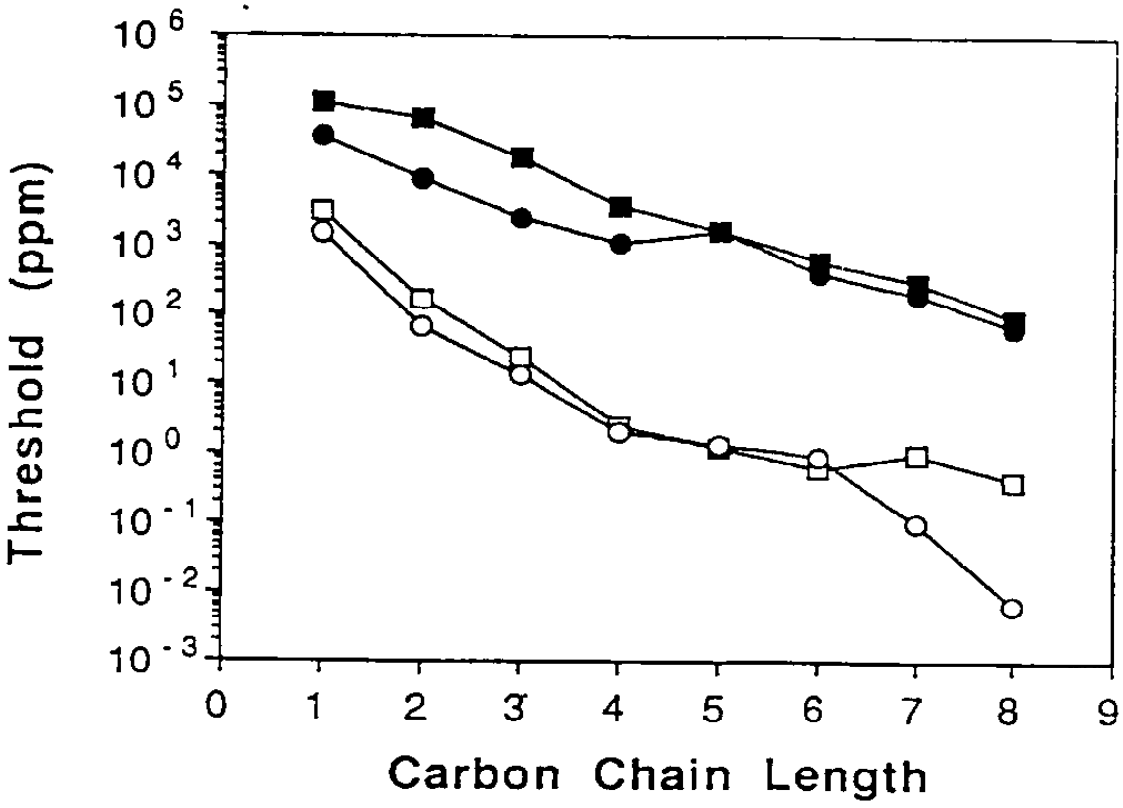


FIGURE 9

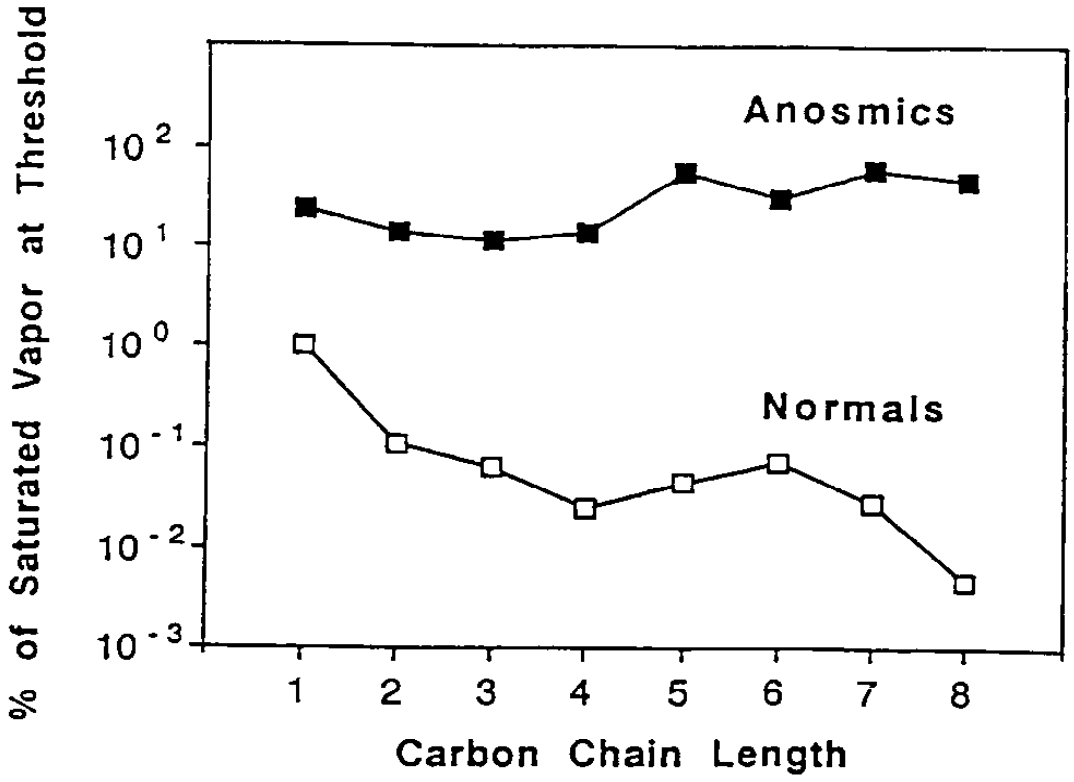


FIGURE 10

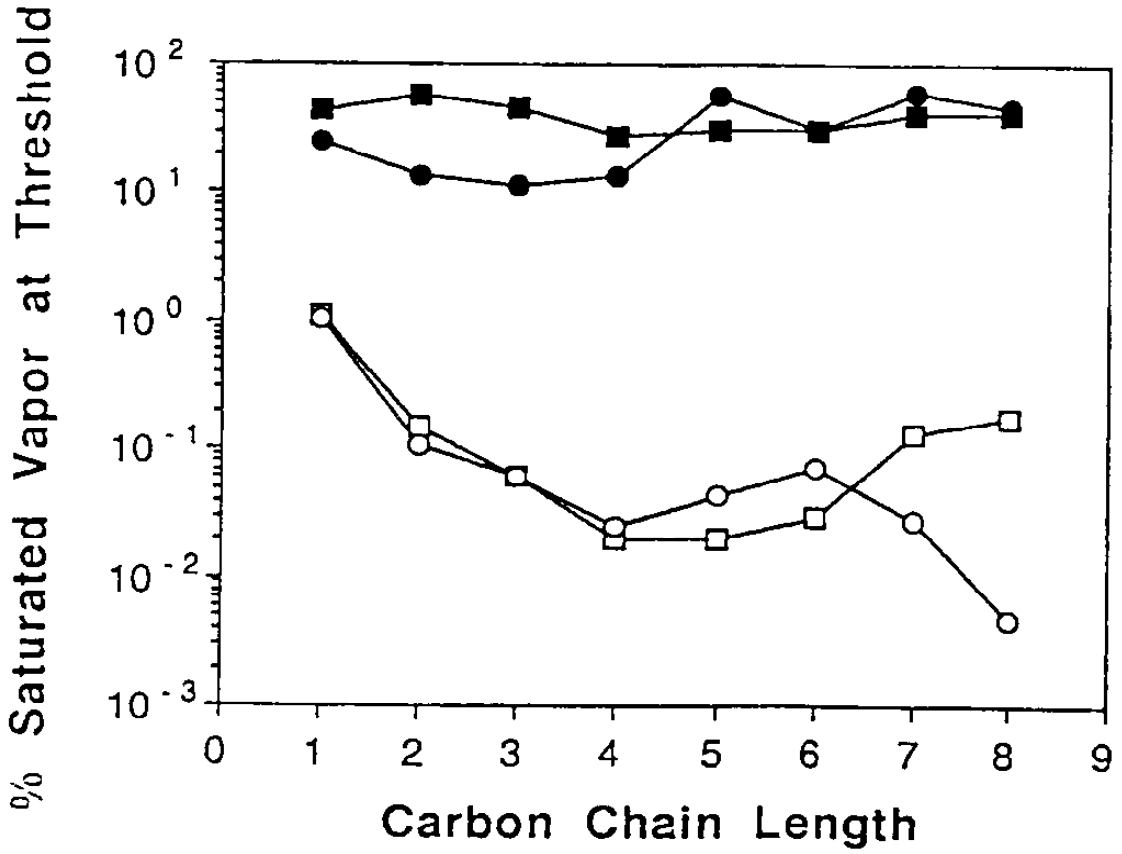


FIGURE 11

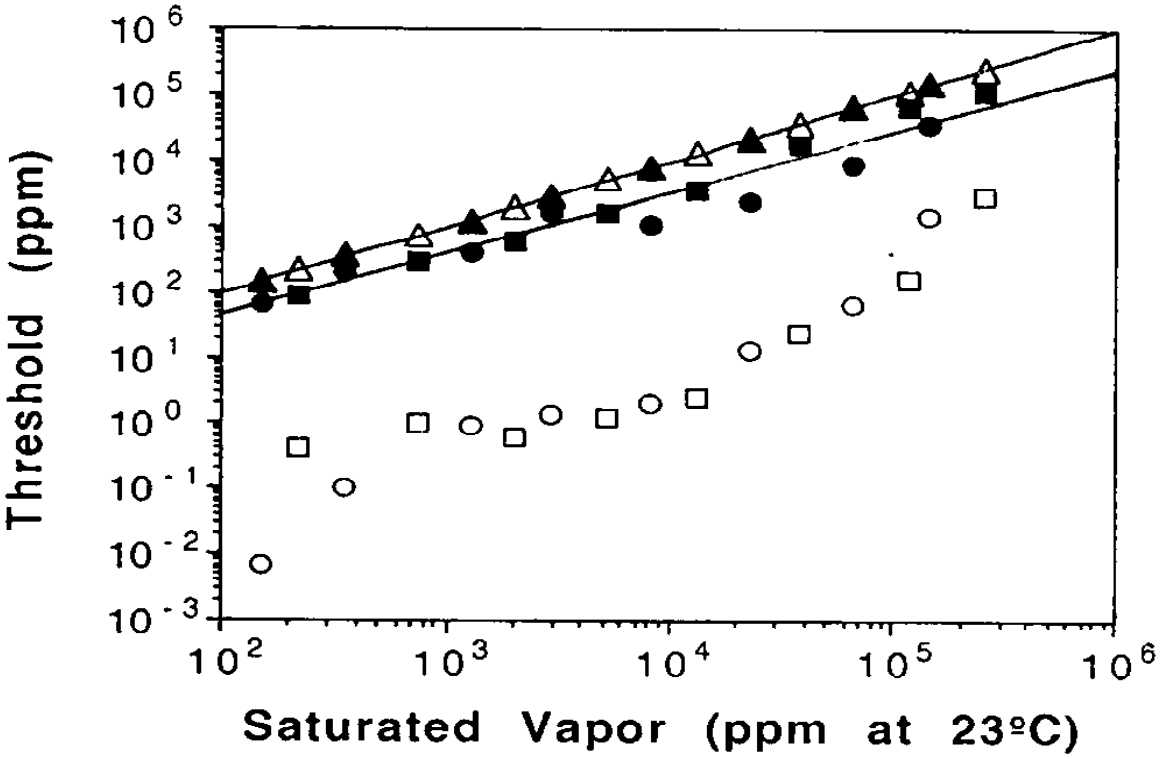


FIGURE 12

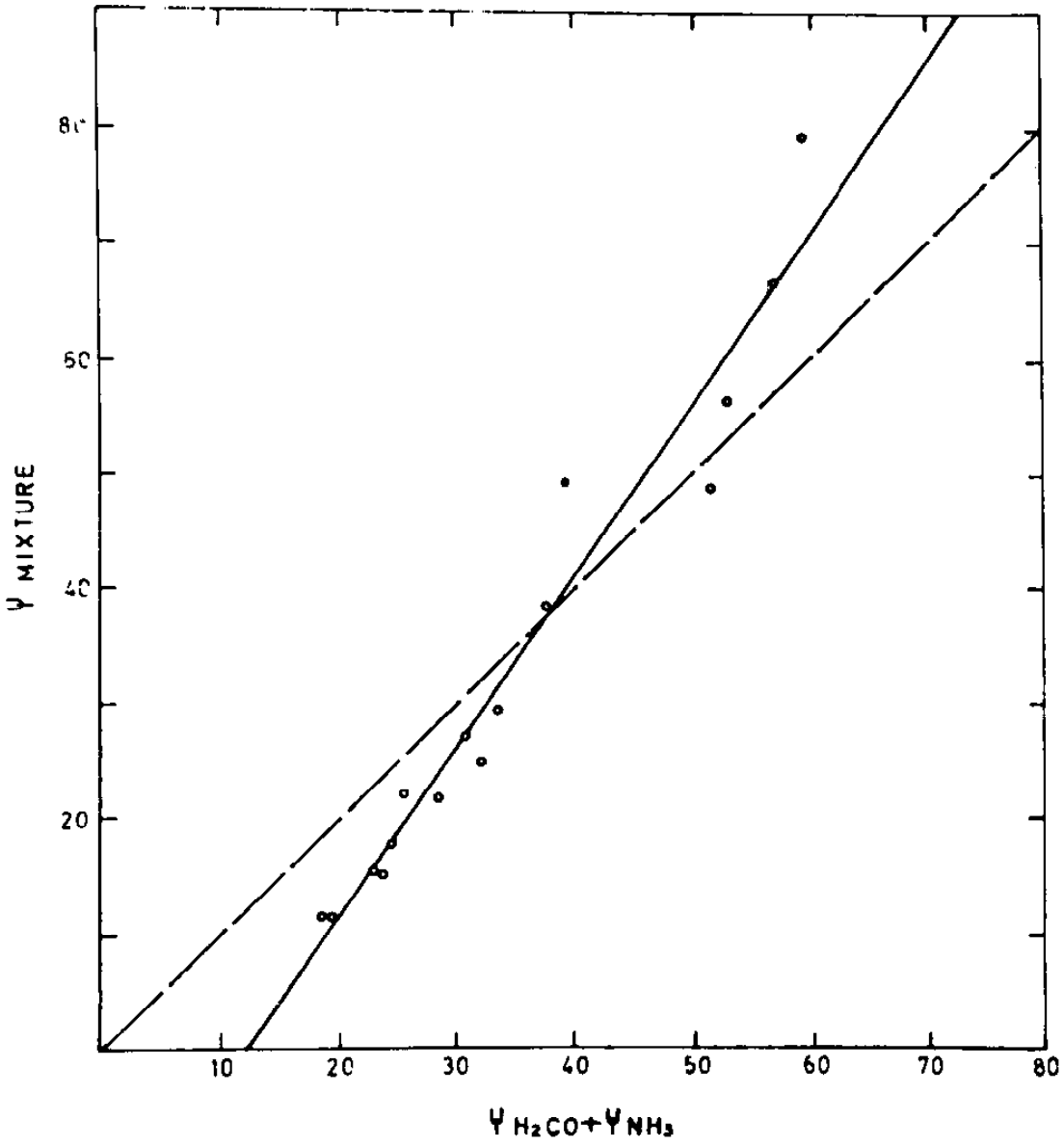


FIGURE 13

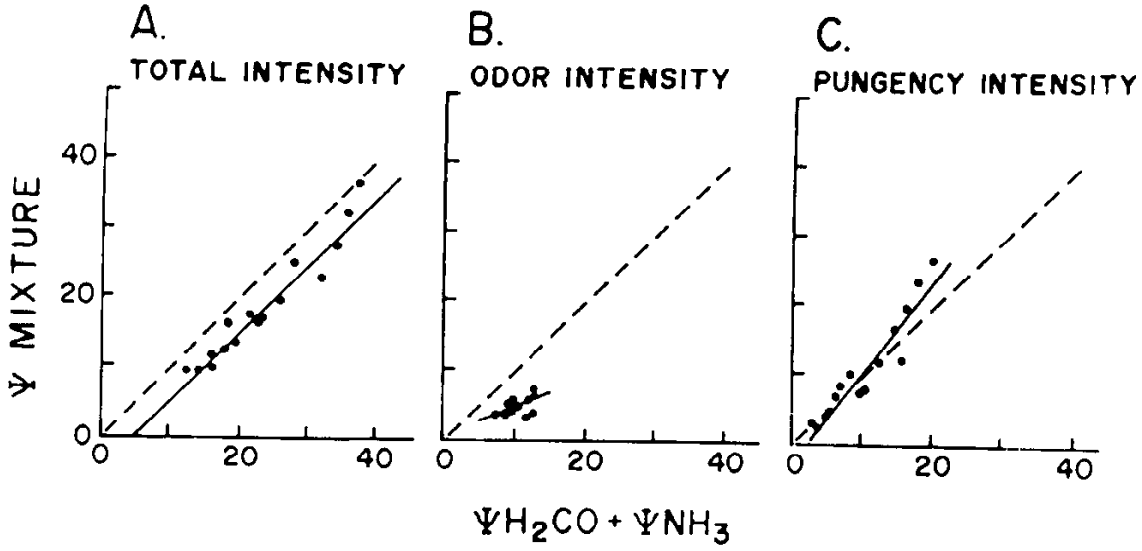


FIGURE 14

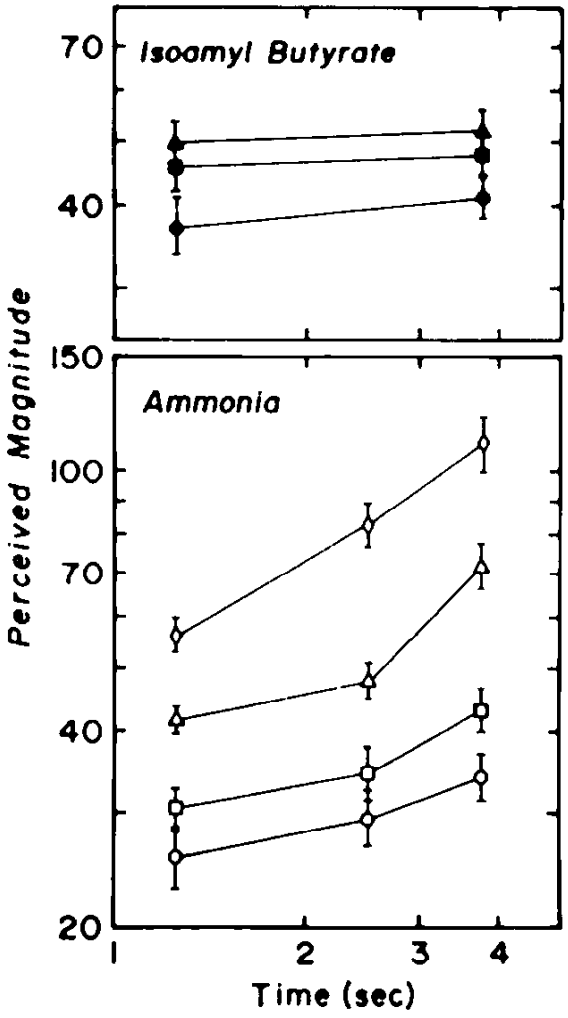


FIGURE 15

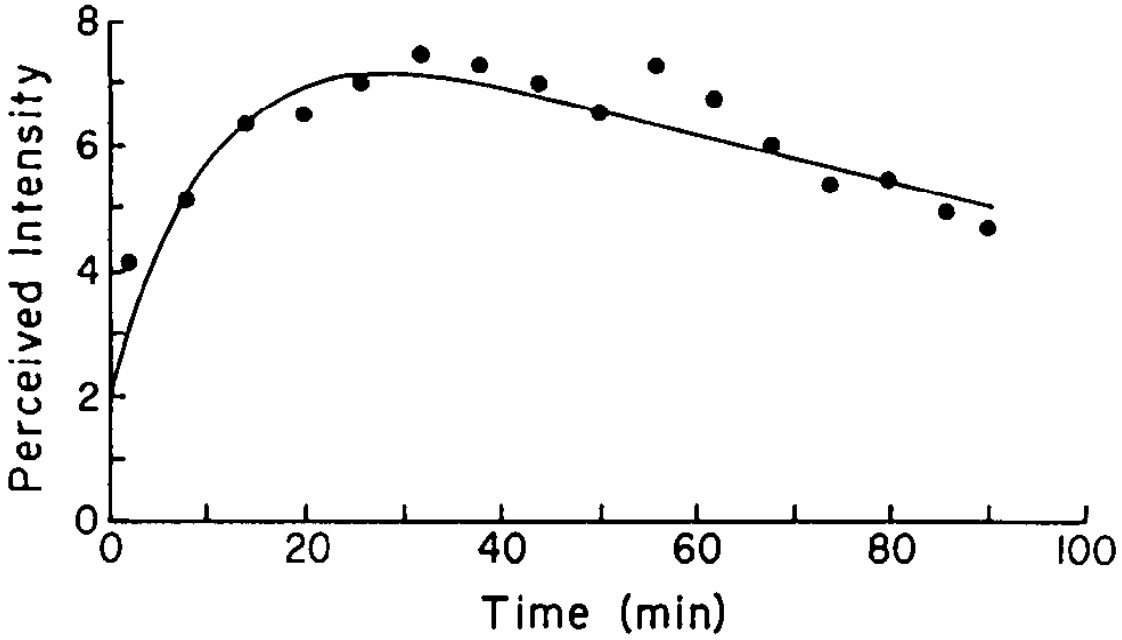


FIGURE 16

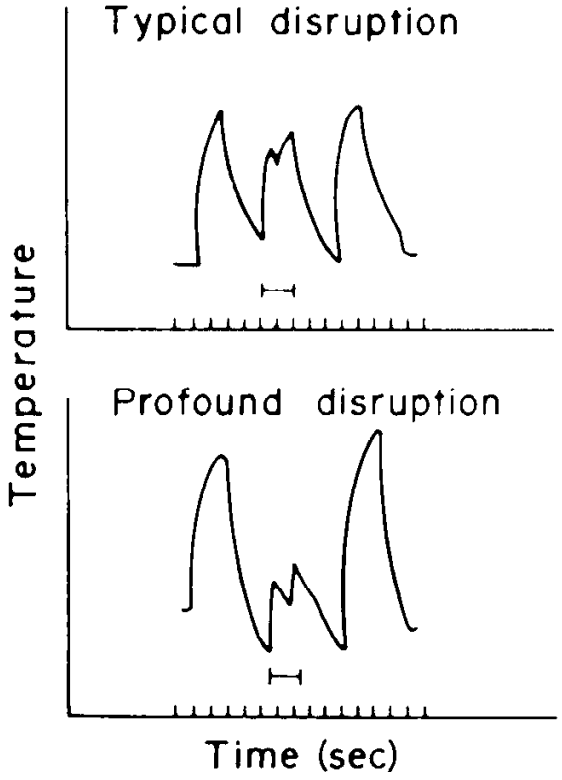
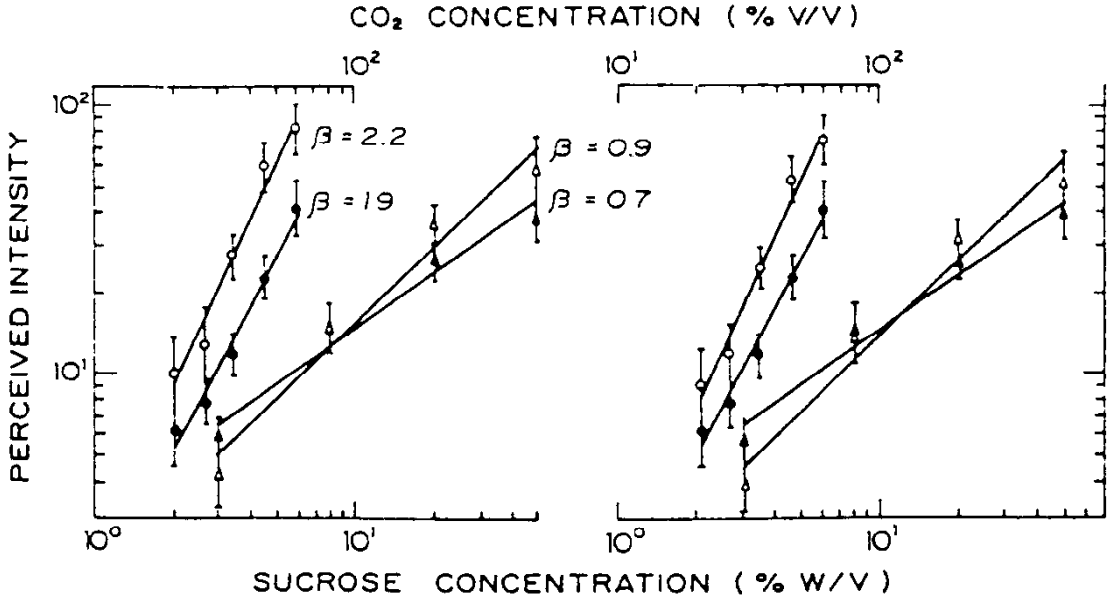


FIGURE 17


CO₂ CONCENTRATION (% V/V)
10²
10¹
10²
10²
10¹
β = 2.2
β = 1.9
β = 0.9
β = 0.7
PERCEIVED INTENSITY
10⁰
10¹
10⁰
10¹
SUCROSE CONCENTRATION (% W/V)