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IRRITATION AND ODOR: SYMPTOMS OF INDOOR AIR POLLUTION

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ABSTRACT

Both irritation and odor figure prominently in complaints about indoor air. Irritation poses the greater problem since it arguably represents an adverse health effect per se and since its sources often prove difficult to locate. There exist various potential assays for irritation, some better for validation of symptoms and some better for research on structure-activity relations. One animal assay, the respiratory depression technique, has produced measures of irritant potency in good accord with psychophysical measurements in humans. Both the animal and human data point toward common physicochemical determinants of potency, especially for the weak irritants that often exist in indoor environments. For the foreseeable future, the assessment of odors in indoor environments will need to proceed as in the past, as psychophysical measurement rather than as chemical measurement. Methodologies for odor measurement continue to evolve. The evaluation of their usefulness in field settings must ultimately stand against a criterion of validity that has proven elusive to set.

INTRODUCTION

Problems of indoor air quality typically become apparent by people's symptoms. Occasionally these take the form of increased bouts or severity of illness, such as colds, but more often take the form of sensory reactions, such as unwanted odors, irritation, and stuffiness. A worker may complain that his throat feels dry, his eyes sting or feel itchy, his nasal passages burn, or that he is offended by mildew odors, food odors, and the like (1). Although not proven, some apparent "neurotoxic" reactions to atmospheric agents, such as memory loss or difficulty of concentration, may result secondarily from the distraction caused by sensory stimulation. Low level irritation may itself prove less apparent than, say, a person's inability to remember information over the phone. The person may consequently feel that poor air quality is affecting his mind directly.

The search for determinants of such conditions as building related occupant complaint syndrome (BROCS) or sick building syndrome (SBS) should obviously build first on the known and then seek to fill in the blanks. Since, as Mølhave (2) noted, "SBS, in brief, is an unexplainable sensory irritation appearing in a large fraction of the occupants of the affected buildings" (p. 47), it is entirely appropriate to focus on sensory irritation. The following will address some of the highlights regarding what is known about sensory irritation. There remain many blanks, but they become smaller year by year.

IRRITATION

• As a sensory event, irritation reflects stimulation of mucosal tissue and reflects a form of chemesthesis, chemically stimulated skin sensation. The nerves that mediate irritation also mediate mechanically and thermally induced sensations. Hence, chemesthesis should have functional properties somewhat like those aroused by these other somesthetic stimuli. A property of particular relevance is temporal summation, i.e., up to a point the longer a stimulus lasts the stronger will be the sensation. Irritation, even if not actually painful, may grow in perceived magnitude the longer a person remains in an irritating environment (3). Nevertheless, somesthetic modalities also exhibit the phenomenon of adaptation, a stimulation-dependent loss of sensitivity. Sorting out the interplay of temporal summation vs adaptation has critical importance, an issue that will come up again below.

• Only the rare volatile organic compound (VOC) lacks the potential to cause irritation. Chemically reactive substances that bind to tissue covalently can cause irritation, but so too can nonreactive substances that bind to tissue physically and reversibly. Both in terms of number of compounds and concentration, the nonreactive substances predominate in indoor air (see, e.g., 4). These are weak irritants, whereas chemically reactive substances are often strong irritants that can invariably stimulate at lower concentrations than their nonreactive analogs (5).

• The reactive chemical properties that cause irritation have long been known in general (e.g., ability to break disulfide bonds, ability to oxidize thiol groups, acid-base reactions), but not necessarily in the kind of detail to allow quantitative predictions of potency (6). In order to learn the potency of any newly relevant reactive irritant, it generally becomes necessary to perform a biological assay.

• As Figure 1 reveals, possibilities for biological assays are numerous. Electrophysiological possibilities, starting with the most peripheral, include the negative mucosal potential recordable from the nasal epithelium in animals or humans (7). Some other potentials, such as action potentials from peripheral nerves, can only be measured in animals (8). Cortical evoked potentials can, however, be measured in either animals or humans (9). Other assays of potential relevance include measurement of neural mediators or modulators, measurement of the products of inflammation, and measurement of reflexes (see, e.g., 10). One can, for instance, look at the presence of polymorphonuclear neutrophilic leukocytes (PMNs) in nasal lavage fluid (11) or can assess the magnitude of a reflex transitory apnea that occurs upon inhalation of a strong irritant (e.g., 12).

Reasons to use biological assays include: 1) evaluation of symptoms, 2) evaluation of potency of stimuli, and 3) ultimate understanding of the biology of irritation. Verification of symptoms of irritation stands unfortunately as a historically neglected area of research. Nevertheless, some recent advances have come from the assessment of changes in the cornea or conjuctiva after exposure to indoor contaminants in both lab and field settings (13) and from measurement of PMNs in nasal lavage fluid of subjects exposed to volatile organic compounds in a controlled setting (11). Such advances merely whet the appetite for more. Verification of a worker's complaint by relatively noninvasive tests would be a major advance. The most satisfying test would constitute a quantitative analysis of, say, a tear or mucus sample, not as a test of a complainant's truthfulness but as a way to monitor a problem. Without verification of complaints, the causes of SBS will remain elusive. It is axiomatic in science that one cannot establish cause without a proper measure of effect.

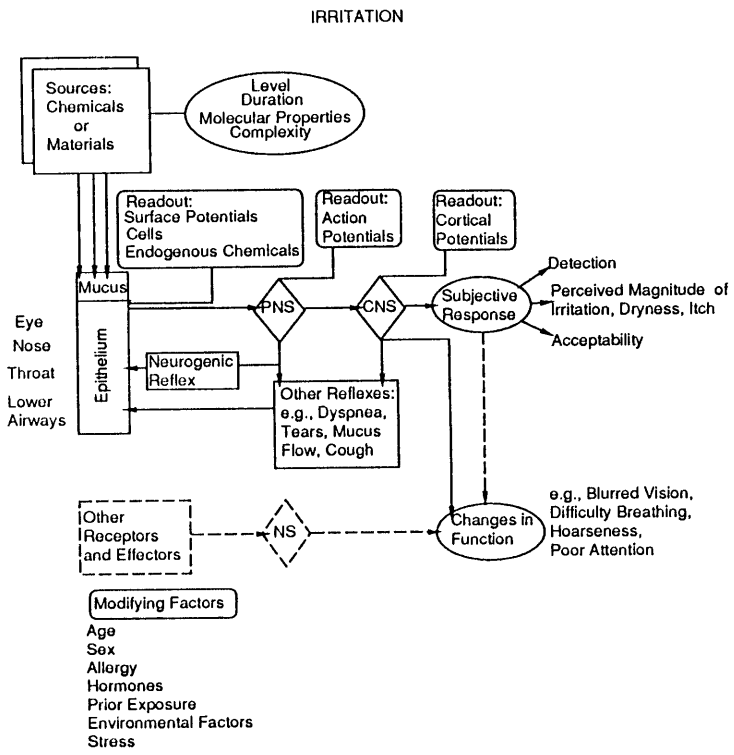

Figure 1. Schema for sensory irritation. Sources or materials may give rise to vapors that reach the eye, nose, throat, or lower airways. A physical description of a stimulus will entail its molecular composition (i.e., what actual species comprise the vapor and in what proportions), its level (i.e., emission rate, airborne concentration, incident concentration) and temporal modulation. The stimulus may come from a continuous or an intermittent source. Depending on the physicochemical properties of the vapors vís-a-vís the epithelium (e.g., partition coefficient between air and lipid or water and lipid), some vapors may initially affect the eyes more than the airways. Some will affect the upper airways more than the lower, etc. Once deposited into mucus, the molecules will either diffuse to a cell membrane, or possibly be carried actively via a transport protein (e.g., odorant binding protein). Steps that occur when the molecules reach the tissue entail at the least: a) ion flow across membranes and measurable via surface potentials, b) immediate secretion of endogenous chemicals such as calcitonin gene related peptide (CGRP) from nerves, or slower secretion of chemicals such histamine, bradykinin, or other intermediaries of inflammation from nonneural cells, and c) in the case of serious irritation, infiltration of cells associated with inflammation (e.g., PMNs). When activated, the nerve endings will create action potentials (spikes) readable collectively as time-averaged activity. Activity in the nerves will set up local reflexes, such as the neurogenic reflex, whereby activity traveling toward the central nervous system (CNS) gives rise to activity traveling toward the periphery along unstimulated branches with subsequent release of possible mediators of irritation (e.g., substance P), or to more remote reflexes such as momentary dyspnea or cough mediated through the central nervous system.. Activity in the CNS could be read as evoked cortical potentials from electrodes on the scalp. Sensations of irritation will have attributes of detectability, magnitude, sensory quality (e.g., pungency, burning), duration, and acceptability. Irritation associated activity, even apart from subjective reactions, can itself alter various body functions. For example, watery eyes may blur vision. Irritation-induced edema in the larynx can cause hoarseness. Subjective reactions may exacerbate changes in function through distraction, stress, or other means. Sensitivity to irritation or its various adverse reactions will vary with various organismic factors, such as age, sex, and stress.

Research directed toward assays of potency of irritants has progressed somewhat farther than that on verification of symptoms. The best known assay, developed by Alarie (e.g., 6), entails measurement of reflex depression of respiratory rate in mice challenged with irritants. The literature contains more than 200 such measurements for about 150 different compounds (14). The concentration that leads to 50% depression of respiratory rate (RD_{50}) forms the common criterion to assess the relative potency of the challenging chemicals. Calculation of the RD_{50} can become complicated by variation in respiratory depression over time. For some substances the depression deepens, whereas for others it rebounds from its initial level even while an exposure continues (see Fig. 2). Despite such complications, in 40 compounds of widely varying potency where local toxicity derived from irritation, RD_{50}s correlated well (r=0.92) with Threshold Limit Values (TLVs) recommended by the American Conference of Governmental Industrial Hygienists (15). This correlation offers the principal validation of the procedure for measurement of relative potency of irritants in human beings. Since TLVs do not arise from a uniform protocol of human experimentation, but rather from consensus derived from any available data, the validation falls well short of ideal. In view of the possibilities for disparity, the level of correspondence is impressive. It would, however, be less impressive if applied just to the weak, mainly nonreactive irritants of principal concern in indoor air.

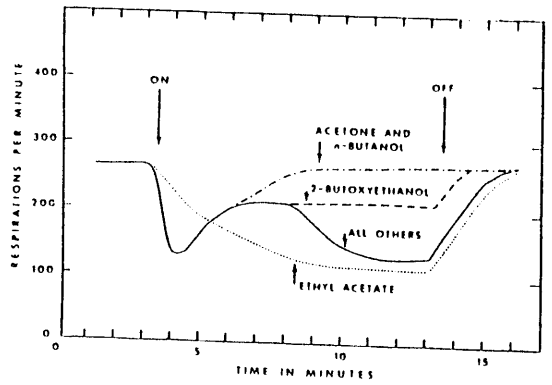

Figure 2. Respiratory rate of four mice before, during, and after exposure to various chemicals. The curve labeled all others contains the results for various alcohols and acetaldehyde. From Kane, Dombroske, and Alarie(17).

The use of the assay for just a single compound holds less interest than its use to explore the physicochemical determinants of irritation. For nonreactive irritants, the assay has yielded some important insights. Abraham and colleagues (16) showed that the partitioning of vapor phase molecules into the liquid phase of the respiratory mucosa correlates very well with the potency of nonreactive irritants. Abraham's quantitative structure-activity model for the phenomenon contains five energy terms that, when added together, represent the net energy required to condense the solute (vapor-phase stimulus) into the solvent phase (mucosa). Correlation coefficients between predicted and obtained values for sets of three to four dozen compounds lie above 0.9. The outcome implies the existence of a nonspecific "receptor" for physical irritants.

• Research in the Pierce Laboratory has focused lately on direct measurement of odor thresholds in persons with normal olfaction and nasal irritation thresholds in anosmics, persons who lack the sense of smell. Anosmics yield virtually pure irritation reactions. Although only a few qualifying persons exist, they fortunately give stable data when studied carefully. The

project has entailed building a foundation of data for a growing list of chemicals - now almost 50. The investigations have incorporated various series of related compounds in the search for relevant physicochemical determinants of potency. This work has produced some very straightforward answers:

- For various series of alkyl compounds, potency increases with chain-length (i.e., the threshold declines), an outcome known already from studies of respiratory depression in mice (17) but not previously demonstrated in humans. Hence, 1-pentanol is more potent than 1-propanol, 2-pentanone more potent than 2-propanone (acetone), n-amyl acetate more potent than n-propyl acetate, etc. (18, 19, 20). People have often thought of the more highly volatile, shorter chain-length members of these series, such as n-propyl acetate and 1-propanol, as the more potent irritants. The illusion comes in part from their higher vapor pressures which makes them more likely to achieve vapor phase concentrations that trigger irritation. A related factor reinforces the illusion: irritation for the more highly volatile compounds becomes apparent at concentrations not greatly above their odor thresholds. For methanol, for instance, irritation begins less than twenty fold above the concentration for odor detection. For heptanol, more potent as irritant and odorant on a molar basis, irritation begins more than three orders of magnitude above the odor threshold. Figure 3 illustrates the point for the aliphatic series of alcohols (19). Our investigation of various series and a few unrelated compounds also suggests a general relationship between odor and irritation thresholds. As Fig. 4 reveals, for potent odorants with thresholds in the range of a part per billion, the irritation threshold lies about four orders of magnitude above the odor threshold, whereas for less potent odorants the irritation threshold lies progressively closer to it.

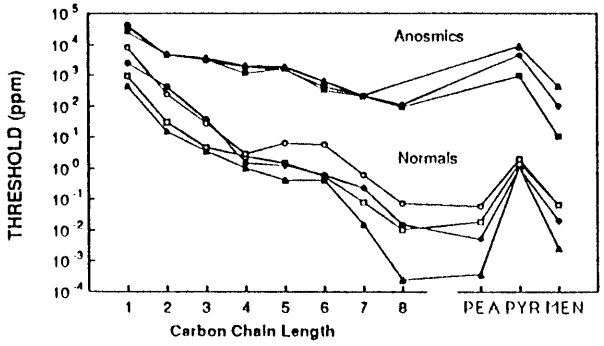

Figure 3. Thresholds for odor (normal subjects) and irritation (anosmic subjects) for the n-aliphatic alcohols from methanol (chain length equal to 1) to octanol (chain length of 8), and for ß-phenyl ethyl alcohol (PEA), pyridine (PYR), and menthol (MEN). Each function shows the data of a single subject tested 12 times with each chemical. From Cometto-Muñiz and Cain (19).

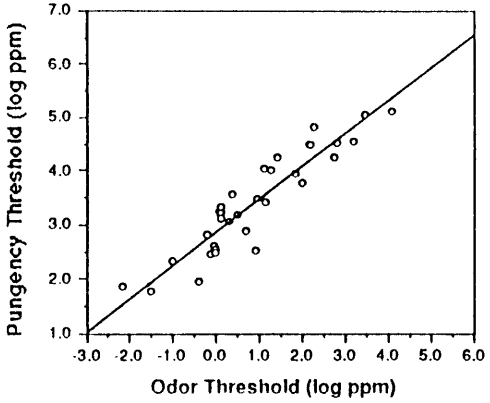

Figure 4. Thresholds for pungency (irritation) vs thresholds for odor for 33 compounds of various chemical and physical properties.

- The irritation threshold declines within aliphatic series much the same way for various series: alcohols, acetates, ketones, and alkyl benzenes. Figure 5 illustrates the agreement for the alcohols and acetates. Measurements on many compounds has prompted the conclusion that the threshold for irritation occurs at constant thermodynamic activity, an outcome essentially consistent with the predictions of Abraham and one that gives reason to believe that specification of the determinants of irritation for nonreactive irritants lies very close at hand. Figure 5 contains the additional information that thresholds for eye irritation occur at similar concentrations to those for nasal irritation (20).

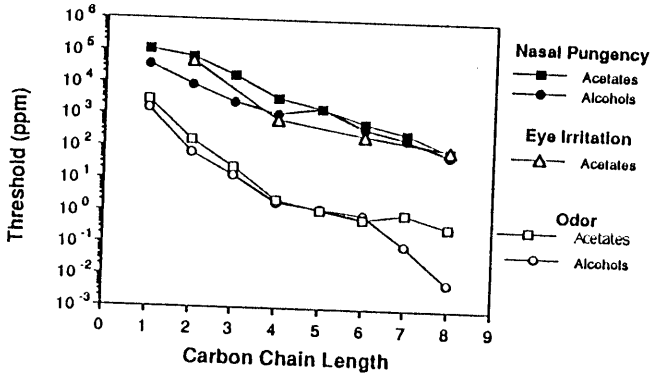

Figure 5. Thresholds for odor and pungency (irritation) in aliphatic alcohols and acetates, and thresholds for eye irritation in the acetates. From Cometto-Muñiz and Cain (12).

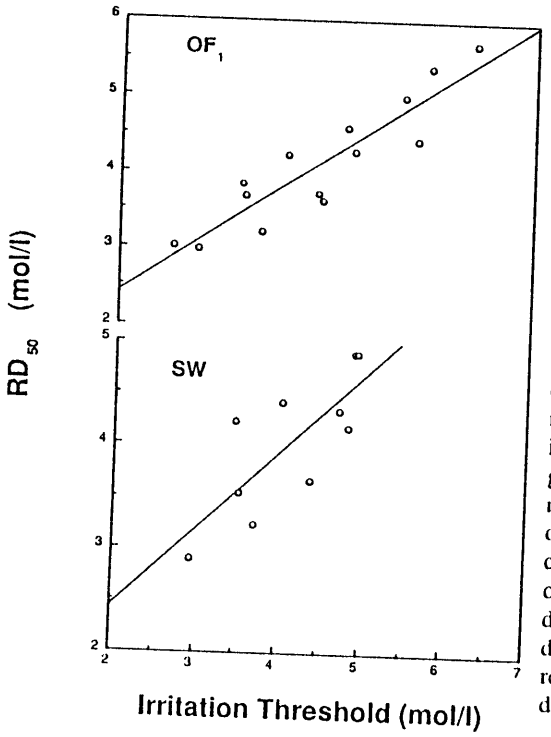

Figure 6. Respiratory depression (RD_{50}) in OF_1 and SW strains of mice (values from the literature) vs irritation thresholds in humans.

- For the RD_{50} to serve as an index of relative potency of irritants for humans, it should correlate with nasal irritation thresholds. Figure 6 shows good correspondence between the human threshold and RD_{50} for two strains of mice. Failure to achieve perfect correspondence merits scrutiny. Some of the disparity may reflect merely random error, a matter that replication can diagnose. Some of it, however, may reflect the complicating influence of duration of exposure. The human measurements reflect instantaneous irritation, perceivable on the first inhalation. These measurements fail to indicate how much worse irritation could become if the person remained exposed. The magnitude of such time-dependent sensitization depends on level of stimulation as well as on duration. That is, time-dependent sensitization for a given compound cannot be characterized by just a single time-constant. This holds for both human and animal exposures.

- In order to screen materials or products for possible inclusion in indoor spaces (21), a reliable animal assay would seem almost essential until supplanted by something else. Hansen, Nielsen, Tøttrup, and colleagues (22) illustrated the promise of the respiratory depression technique in recent exposures of mice to dried paints and lacquers. Nevertheless, the animal data must stand against a template of human results. Which human assay will prove best requires more exploration. Eye irritation, for example, has the advantage that exposure can last relatively long without the possible systemic risks entailed in breathing irritants. Further comparison of nasal and eye irritation thresholds should focus on their interchangeability.

ODOR VS IRRITATION

Irritation differs from odor in its relatively uniform quality, though it does show some variation. Molecules of shorter chain-length, for example, commonly exhibit a sharper bite than those of longer chain-length, which produce more burn than bite. This difference may occur because of where the molecules deposit themselves in the airways, such as concentrating themselves in the anterior part of the nasal cavity, which short chain-length molecules do, vs spreading themselves over wider surface areas, which longer chain-length molecules do.

The relative perceptual uniformity of irritation has both a good and a bad side. On the good side, lack of variation in quality simplifies the quest for understanding. For mixtures, for example, components may simply add their respective effects. This notion already has some support and some theoretical justification, but would prove a powerful and useful generality if fully supported (5). It would mean that substances present below their own thresholds would contribute to irritation in a manner proportional to their thresholds. Indoor air may contain scores or hundreds of potentially irritating VOCs at concentrations below their respective thresholds. Knowledge of their thresholds and a generic rule for additivity would allow prediction of when such a mixture would achieve a net detectable level of irritation. What we could call the "weighted efficacy of a mixture" might account for many instances where no single compound can account for the irritation experienced in a space.

On the bad side, the perceptual uniformity of irritants obscures their sources. When people experience irritation in a space, they often cannot tell what to control or eliminate. (If the irritation comes from the net influence of many VOCs, elimination of no single source would ameliorate it anyway.) Odors, which can vary widely in perceived quality, do indicate their sources. Only tobacco smoke smells like tobacco smoke, only car exhaust smells like car exhaust, etc. Hence, odors generally prove more diagnostic of particular problems. Nevertheless, the very varied quality of odors makes olfaction a considerably more complicated sensory system to understand.

ODORS

Odors play a complex role in indoor air quality. In the absence of better means to decide the healthfulness of indoor spaces, the nose has historically guided ventilation practice, from the

mid-nineteenth century to Yaglou sixty years ago to the present day (23). Researchers have formalized its role in chamber experiments on such notable contaminants as occupancy odor, tobacco smoke odor, and even the odor of dust (24). Early on, it became apparent that one cannot ventilate spaces with levels of outside air high enough to achieve a criterion of no odor. Hence, visitors fresh to a space, the "model persons" seen as most sensitive and therefore as most relevant, must tolerate some odor, but presumably not objectionable ones. Fortunately, levels of ventilation that have achieved acceptable levels of odor have often apparently controlled other insensible contaminants rather handily. Therefore, what has satisfied the nose has commonly "satisfied" the rest of the body.

Odors distinguish themselves from many other forms of simple sensations such as sounds or sights by their marked hedonic effects, i.e., their pleasantness and unpleasantness. No other sensation could empty a room faster than a disgusting odor, even when only moderate in intensity. The determinants of olfactory-induced disgust or even just simple unpleasantness have received little research attention, but generally seem to involve odors of decomposition and of bacterial action. Bad breath, flatus, stale urine, armpit odor, and the odors of rotting flesh, rotting dairy products, and rotting vegetables constitute the classic malodors. The message they send is "Don't eat me, for you may become ill," rather than "Don't breathe me." As far as anyone can tell, although malodors may nauseate people and even make them vomit, they do not cause disease. If they did, then workers in palpably malodorous operations either would not stay well very long or would qualify as "bionic" for their ability to withstand the challenge. Furthermore, everyone knows the converse situation that pleasant odors may belong to some deadly poisons.

Lack of a connection between odors and illness does not alter the simple fact that people do not want inappropriate odors in their environment and may be repulsed by them. The term inappropriate seems most relevant here since context plays a big role in perceived pleasantness, e.g., people may find the odor of a locker room unobjectionable in a locker room though not in a reception area. Although inappropriate odors may often lead to diagnosis of a problem, i.e., a strange smell appears and makes occupants uneasy enough to search for a particular source, sometimes the odor level reflects poor general housekeeping and a relatively high background of nondescript quality. Surprisingly, against a high background level some malodors become more pronounced and a poor situation becomes disproportionately worse.

The principal issue regarding odors is how different chemicals give rise to qualitatively different odor experiences - some good, some bad, some acceptable, and some not. In this respect, issues regarding the odor environment resemble those regarding the sound environment. People in an office may tolerate some ambient sound, but not excessive sound. The task of noise abatement involves in part control of the general level, but also control of particular sources. Just as each noisy object in the office environment, e.g., a printer or photocopier, has a unique spectrum of sound emissions, each olfactory "object," e.g., a carpet or a moldy area under some wall covering, has a unique "spectrum" of olfactory emissions. Just as the characteristic sound of a photocopier arises from energy present at many sound frequencies, the odor of a carpet usually comes from many chemicals.

It would take many years to characterize the chemical signature of every olfactory object in the environment and to figure out the contribution of each compound in the signature to net perceived level and quality. The foreseeable future accordingly will require dealing with the chemical emissions of objects in olfactory terms per se, i.e., as olfactory objects. The many

thousands of odor-relevant chemicals could not be distilled to a list of a few score, with relevant concentration limits and with some assurance of successful control over all conceivable odor problems. Like it or not, the evaluation of odor control requires the nose that comes attached to a person, with likes, dislikes, biases, capabilities, and so on. The research agenda regarding the sense of smell and indoor air quality would seem best focused both on whether some noses are harder to satisfy than others (e.g., Do people who define themselves as allergic have different sensitivity than others?) and on how to put the nose to work in odor evaluation in a scientifically productive way. The question of odor evaluation involves the development of methodology.

Within the last fifteen years, various psychophysical methodologies have seen use in laboratory investigations of indoor air quality and ventilation requirements. In general, these investigations have entailed the use of untrained observers who make judgments of the odor intensity and acceptability of, for example, environmental tobacco smoke. Within the last five years, Fanger (e.g., 25, 26, 27) has proposed a variant of earlier methodologies. In its current version, Fanger's "olf" method involves the use of trained observers who make acceptability ratings which they express in terms of concentrations of acetone (2-propanone). By certain assumptions, these concentrations of acetone are translated into the percent of typical people who would be dissatisfied with the odor that the observers experienced.

The olf method has seen use in the laboratory and in the field. Its latter application has received the most notice, for it is the only procedure currently used in the field mode. It would be desirable to judge that method or any other proposed method against a criterion of validity: the proportion of people in a building predicted to be dissatisfied versus the actual proportion dissatisfied. Unfortunately, such a criterion of validity has proven elusive. Field studies of the normal occupants of buildings seem to get over-reporting of dissatisfaction. Accurate measurements of the criterion of validity are a prerequisite for meeting it. This is hardly a trivial concern, for if a methodology implies that 20% of the persons in a building will be dissatisfied and there is no way to confirm it, then users become slaves to the methodology. In the absence of a firm criterion of validity, a criterion of converging lines of evidence gathered by independent means offers the next best way to establish the usefulness of any proposed psychophysical procedure for broad field use.

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INDOOR AIR '93

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Volume 1. Health Effects

CONFERENCE SECRETARIAT

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