Health Effects of Indoor Odorants
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Introduction

Odorants, along with irritants, allergens, molds, and bacteria, are the “pathogenic messengers” of improper design, construction, and maintenance of building ventilation systems (1). Several factors have been identified that make odor control a primary goal of ventilation engineers and building designers (2): modern buildings permit less infiltration through walls; outdoor air is often odor polluted; high energy costs have reduced ventilation rates at the same time that the public is becoming less tolerant of noxious odors (e.g., cigarette-related odors).

Instead of correcting the problem at the source, building managers and home owners may resort to quick fixes, installing “air fresheners” and “deodorizers.” These devices emit organic compounds, including nonane, decane, undecane, ethyheptane, pinene, limonene, and substituted aromatics such as para-dichlorobenzene (3), which has become one of the leading volatile organic compounds (VOCs) in indoor air (4).

This paper addresses current understanding regarding mechanisms of olfaction, types of odorants, means of measuring odorants, and known health effects associated with indoor odorants.

Mechanisms of Olfaction

Olfactory function takes place in olfactory receptor cells located in the olfactory epithelium. Four cell types are present in the olfactory epithelium: sustentacular cells, olfactory receptor cells, basal cells, and microvillar cells (Fig. I).

Sustentacular cells possess microvilli at their luminal membranes. These cells contribute to nasal mucous production, as well as serving as electric insulators of the olfactory neurons. Olfactory receptor cells are small, bipolar neurons that send a dendrite toward the nasal lumen and an axon toward the olfactory bulb. It is likely that, initially, transduction events occur at the plasma membranes of the olfactory cilia after the odorant has diffused through the mucous layer. Basal cells are cuboidal cells adjacent to the basement membrane. These are progenitor cells for the olfactory receptor neurons and maintain a unique degree of plasticity, allowing for near-complete recovery despite damage to the olfactory epithelium or transection of the olfactory nerve (5). Microvillar cells are flask-shaped cells that have a tuft of short microvilli projecting from the apex of the cell (6).

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It has been a major challenge to understand the precise mechanism of olfaction. How do we recognize thousands of different odorants at concentrations as low as 1 part per trillion? How do we explain specific anosmia, whether inherited or acquired?

The nature of the odorant receptors is still unresolved. One theory suggests that specific odorant receptor proteins might mediate the recognition of odorants (7). A pyrazine binding protein has been identified in cows, which is homologous with α-microglobulin, which belongs to the family containing retinol-binding proteins (8). As yet, the significance of these soluble odorant-binding proteins secreted into the mucus and which bind odorants with low affinity is not clear. Snyder et al. have localized the odorant-binding protein (OBP) to the lateral nasal gland (9) and suggest that the OBP appears to be atomized into incoming air, at the tip of the nose, and might trap odorants and carry them to the area of the olfactory epithelium. Alternatively, OBP might serve as a filter, protecting receptors from too high concentrations of odorants (10).

Olfactory transduction likely involves a complex interaction with several mechanisms in the cell (Fig. 2). Cyclic AMP likely plays a key role. A GTP-binding protein that mediates stimulation of adenylate cyclase, the Golf protein (11), is expressed only in olfactory receptor cells. It has been observed that the adenylate cyclase pathway mediates olfactory transduction for a wide variety of odorants (12). It has been hypothesized that odorant-induced influx of calcium initiates the sequence of events that leads to excitation of the cell (5). Olfactory receptors then likely respond with an increase in membrane conductance, leading to membrane depolarization and generation of action potentials. Several hundred olfactory axons connect with specific individual cells in the olfactory bulb to form the olfactory glomeruli, which, each function as a unit, either responding or not responding to a specific odorant stimulus (7).

Olfactory information is then transmitted to several regions of the brain, both cortical and subcortical. Some areas receiving olfactory nerve input are associated with memory formation and retrieval, and others are involved in the modulation of emotional responses (e.g., the limbic system) and still others in the regulation of neuroendocrine function (e.g., the hypothalamus) (13).

There is apparent variability of genetically determined specific anosmias in the general population. For example, 40 to 50% of adults cannot detect an odor of androstosterone, a volatile steroid found in sweat, bacon, truffles, and celery. However, perception may be induced in half of those who are specifically anosmic by repeated exposure over a 6-week period (15). Odor perception reduces with age, but some odorants are resistant to aging effects: eugenol and rose (13). Odor pollution may augment the effects of aging (13).

### Indoor Odorant Types

Inorganic chemicals are generally odorless, with the exception of sulfur-containing compounds and ozone. Organic chemicals with molecular weights more than 300 are generally odorless due in large part to their low vapor pressures (2). Other organic materials are generally odorants, some being detectable at airborne concentrations as low as 1 part per trillion. The most frequent reason for establishing a threshold limit value (TLV) by the American Conference of Government and Industrial Hygienists (ACGIH) is to prevent sensory irritation, an end point that varies in its relationship to odorant potency across different compounds (14). Several authors have compared odor thresholds to occupational airborne standards for chemical substances and shown that for some chemicals the margin of safety is low or nonexistent between the odor threshold and the maximal allowable concentration or threshold limit value (15,16). Relevant odors are generally mixtures of compounds, not individual chemicals.

### Occupant-Produced Odorants

Occupant-produced odorants are the most obvious indoor source but most difficult to define, either in terms of constituents or significance. In the nineteenth century, many people believed that the substances given off by the human body were harmful (17). Recommendations for indoor air ventilation rates were initially set based on prevention of body odor from occupants of buildings (18). Thus, early research on indoor air quality tended to focus on body odor. Yaglou et al. (19), at the Harvard School of Public Health in 1936, concluded that the control of body odor would require a ventilation rate of 7 to 25 cfm (cubic feet per minute) per occupant.

There is no current method of measuring such odor, other than by human panel studies of expert judges of air quality. Human body odors have been quantitated in terms of the “olf,” which is the amount of air pollution produced by the average person (20). Another quantitative unit of odorants is the “decipol,” which is the perceived level of pollution produced by the average human ventilated by 10 L/sec of unpolluted air or its equivalent level of dissatisfaction from nonhuman air pollutants (21).

Recent research has determined that the ventilation rate needed to control occupancy odor to a criterion of 80% acceptance equals approximately 17 cfm (8 L/sec) per occupant (17).

### Perfumes and Other Commercial Odorants and Deodorizers

The perfume and cosmetics industry is built on stimulation of human response through odorants. Perfumes are organic compounds which, either by themselves or combined with other
substances, are intended to produce a pleasant olfactory sensation when present in either concentrated or dilute form (22). Deodorizers and air fresheners are commonly used for purposes of odor masking in residences and restrooms of office and other buildings. These may contain nonane, decane, undecane, ethylheptane, limonene (3), or paradichlorobenzene. Perfumes may be either unique or complex, natural or synthetic. Very little is known about the toxicity of many of the constituents of perfumes at the levels encountered environmentally.

Allergy is the most commonly reported health effect of some perfumes, but as discussed below, perfumes are one of the most commonly reported exacerbating agents for asthma (23) and “multiple chemical sensitivities” (24).

**Odorants from Building Materials: Aldehydes and Solvents**

Formaldehyde is often cited as a likely indoor odorant/irritant responsible for health complaints in building illness outbreaks. It is sometimes present at near-TLV levels in homes as well as offices, resulting in higher biological plausibility for toxic or irritant effect than other odorants present at levels orders of magnitudes below the TLV in such environments. However, most odor pollution problems in buildings result from other volatile organic chemicals or other chemicals: carpet glues, caulk, paint solvents, insulation, workstation panels, and other building materials or furniture (3).

**Case Example.** After the opening of a new elementary school in the fall of 1986, several members of the school staff noted symptoms they attributed to the workplace (25). An investigation by the state Occupational Safety and Health Administration found no major health problem and concluded that fireproofing at the school may have caused a petroleum-like odor. The problem continued (with children and staff complaints of headache, dizziness, abdominal pain, cough, and runny nose with itchy eyes), and the National Institute for Occupational Safety and Health performed sampling that confirmed that the odorant was from the fireproofing. A sealant was applied, but complaints of the odor and illnesses continued. Subsequently, air ventilation rates were found to be poor, resulting from design inadequacies. Fireproofing material was also found to have been sprayed inside the return air ventilation ducts. Once ventilation rates were improved to above American Society of Heating, Refrigeration and Air Conditioning Engineers (ASHRAE) standards and fireproofing removed from the ducts, both symptoms and odor complaints were markedly reduced.

As this case illustrates, it is often difficult to separate the effects of odorants from those due to accumulation of other organic compounds in poorly ventilated buildings, and correction of both may be needed before a problem can be resolved.

**Reentrained Odorants from Outdoor Air: Motor Vehicular Exhaust and Industrial Process Odorants**

In building illness investigations, reentrained outdoor air is a common cause of odor complaints. Exhausts, flat roofs, eaves, vent stacks, chimneys, evaporative coolers, and cooling towers are sources of odors or bioburden that can permeate and foul entire ventilation systems. Air intakes are often located at ground level due to concern about avoiding smoke entrainment in building fires. This often results in air intakes adjacent to car or truck parking areas, producing frequent complaints of indoor odorant pollution. Careless location of air intakes near a neighboring hospital’s waste processing area in a Massachusetts hospital resulted in odor complaints (1).

**Bio-odorants: Mercaptans and Other Sulfur-Containing Compounds Resulting from Organic Materials, Molds, and Foods**

Bio-odorants are one of the most frequent causes of indoor air pollution, primarily due to poor humidity controls resulting in overgrowth of molds and change of mold species pattern in buildings (26). Other bio-odorants may be found in buildings where animals are kept (e.g., veterinary hospitals, zoos), or where animals have invaded (bats, rats, mice). We have recently investigated a major outbreak of indoor odorant-related complaints in a veterinary medical school where animals were kept in a large animal barn and throughout the school and hospital. A combination of molds and animal odorants, as well as a poorly designed ventilation system, likely resulted in the problems we found. Solutions to such problems require physical separation of animal living quarters from human-occupied buildings, elimination of ventilation cross-contamination with animal-derived odors, control of humidity, elimination of fiberglass insulation on the inside of ventilation ducts (which served as a physical substrate for mold growth), and replacement and prompt repair of a constantly leaking flat roof.

**Smoke-Related Odorants**

Many people now perceive environmental tobacco smoke (ETS) as injurious to health (27). Several experiments have identified cigarette smoke as a key factor in the acceptability of indoor air. Cain (17) has studied perceived odor intensity and acceptability during smoking and nonsmoking situations in an aluminum chamber. Judges smelled chamber air from outside. In contrast with Yaglou et al. (19), Cain found no impact of crowding, if ventilation rate per occupant was maintained constant and thermal control was maintained.

Under the most severe conditions of nonsmoking occupancy, with and hot, humid conditions and little ventilation, the judges in the Cain study found odor intensity to be about equal to 128 ppm of 1-butanol (the standard recommended by the American Society for Testing and Materials). When smoking was added, judges found the odor to reach as high as the equivalent of 512 ppm 1-butanol (27).

A total of 4230 ft³ (120 m³) per cigarette smoked was found to be needed to reach 80% acceptability in terms of odor. Under the assumptions of Cain (27) regarding prevalence of smoking and length of time each cigarette was smoked and assuming that 10% of smokers would be smoking at any one time, the ventilation rate required would be 53 ft³ cfm/occupant (17). Thus, the current minimum ASHRAE standard of 20 cfm/occupant is most likely inadequate to control odors from cigarette smoke. Due to the low odor threshold for constituents of ETS, the ventilation requirement to control odors is estimated to be about 10 times higher than that required to control irritant effects (28,29).
Cain (27) found that intensity, not quality of odor, was key to cigarette odor complaints. Nonsmokers are much more likely to object to cigarette odors than smokers. For example, at 32 ppm, only 1% of smokers found it objectionable, while 20% of nonsmokers found it objectionable. Cain (27) concludes: “In terms of practical solutions to the odor problem caused by tobacco smoke, the difference between smokers and nonsmokers may prove insurmountable. Under realistic levels of smoking, no realistic level of ventilation will drive tobacco smoke odor to a level as low as the equivalent of 32 ppm butanol.”

Mixtures of Odorants

Little is known of the mechanism of interaction of odorant mixtures resulting in the perceived quality and intensity of the mixture. A recent technique using radioactive 2-deoxyglucose has been used to test the effects of two-component mixtures in rats. It was found that the processing of odor mixtures occurs early in the odorant processing steps, either at the nasal receptor sheet or within the olfactory glomeruli (30).

Mixtures may result in counteraction, independence, addition, masking, and synergism (31). Berglund and Berglund (32) reported that odor mixtures that are homogeneous may be modeled as simple vector addition. Homogenous odors are odors that, when mixed, result in a new odor quality so that the individual constituents are not perceived in the mixture. The odor strength of mixtures formed from two to five constituents of equal strength only slightly exceeds the odor strength of the individual odorants (33).

Relative Contribution of Various Sources to Indoor Air Quality

A study of 15 randomly selected offices in Denmark using a panel of judges to assess air quality, including odor, found that 20% of the perceived air pollution was due to building materials, 42% to the ventilation system, 25% to smoking and other occupant activities, and only 13% to occupants (e.g., body odor) (21). It is not clear what proportion of each of these reflect effects of odor as contrasted with those of irritation.

Methodology of Measuring Odorants

Odor Threshold

Odor detection thresholds may be defined as the lowest concentration perceived by a single subject (absolute threshold), or as the concentration at which 50 or 100% of a panel of subjects notice an odor. Odor recognition thresholds are similar, but involve the end point of odorant identification. Mixtures of chemicals may produce odors that are completely independent of each other, with additive, suppressive, or synergistic effects (34).

Human Panels

Dravnieks (35) wrote extensively on the use of odor panels, particularly in outdoor air pollution research and abatement. Panels are frequently used by air quality management districts to judge odor intensity and hedonic tone (acceptability and how an odor is perceived on the scale of pleasant versus unpleasant) or annoyance qualities (36). Panels should be selected to reflect the broad range of population sensitivities, with at least seven panelists per panel to allow statistical methods to be used (37).

Measurement Scales

Nominal scales have been used to judge quality of odorants. Ordinal scales, formed by rank ordering, have been used to measure odor pleasantness (38). Objective interval scales, using equal intervals such as those used for temperature, have not yet been found useful in measuring odor intensity or quality. However, perceived interval scales, such as the method of magnitude estimation individualized to the subject, are widely used in psychophysical experiments (39,40). Such a scale may be developed by free assignment of a number (any number) to each of several odors. Ratios of numbers in such a scale are then considered to be ratios of perceived intensities. Serial dilution has been most often used by various bottle-based olfactory threshold testing measures.

Clinical Epidemiological Evaluation of Olfaction

Recent reviews of methods of clinical evaluation of patients with olfactory dysfunction have been published (41,42) and will not be summarized here. In general, two methods have been used: a) identification of a different distribution of olfactory thresholds in an exposed population, compared with an unexposed population; b) estimation of the prevalence of specific anosmias using odor-identification testing in exposed and nonexposed population-based studies with “scratch-and-sniff tests.”

Health Effects of Odorants Found in the Indoor Environment

Loss of the Sense of Smell: Hyposmia and Anosmia

Does chronic exposure to odorants result in loss of olfactory function? Few data have been published on this area. Naus (43) found that exposure to menthol reduces the worker’s ability to detect test odors. Emmett (44) has noted that “Certainly the number of materials described as causing olfactory disturbances is large, suggesting an analogy between the loss of smell in chemical workers and loss of hearing in workers exposed to noise.” We have studied the carbinal threshold of painters exposed chronically to paints and solvents, compared with plumbers, and found a significant increase in olfactory dysfunction among older painters compared with older plumbers (45). We have recently completed a study of olfactory function among solvent-exposed microelectronics workers and found a significantly increased prevalence of olfactory dysfunction and significantly higher olfactory thresholds compared with unexposed referents matched on age, sex, race, and cigarette smoking (46). Amoore has published an encyclopedic review of chemical agents associated with acute or chronic olfactory dysfunction (47).

Nonspecific Effects

Malodors may be cited by persons as a cause of digestive disturbances (anorexia, nausea, vomiting, gagging), central
nervous system symptoms (dizziness, lightheadedness, lethargy), and headaches (48). Both innate odor aversions (49) and classical conditioning have been cited as potential mechanisms of inducing these nonspecific effects (50).

**Behavioral Sensitization to Odorants**

The problem of intermittent symptoms temporally related to the perception of chemical odors is encountered by occupational and environmental health practitioners. Every-day experience tells us that strong and unpleasant odors may be accompanied by marked visceral responses. Clinical and epidemiologic experience highlights the fact that some people experience a variety of symptoms when exposed to chemical concentrations deemed likely to elicit only mild to moderately intense odor sensation. Estimates of the population prevalence of increased sensitivity to chemical odors range somewhere above 15% (51). Likewise, while many chemicals have odor thresholds orders of magnitude lower than their irritant thresholds (34), some individuals respond with symptoms at odorant (but subirritant) concentrations of these same chemicals. Is this simply due to wide variation in innate interindividual sensitivity (e.g., odor or irritation thresholds), or is some other mechanism involved? A variety of mechanisms have been proposed to explain the triggering of symptoms by levels of exposure that have been historically considered toxicologically trivial. These mechanisms include “acquired intolerance” (to pesticides (52) or solvents (53)), “olfactory vertigo” (54), “psychological sensitization” (55), “panic disorder (in response to solvents)” (56).

We have evaluated cases of recurrent hyperventilation-like symptoms after acute overexposures to irritant chemicals. In each case, the chemical’s odor was tolerated before the acute overexposure but triggered recurrent panic or hyperventilation symptoms thereafter. One such subject developed symptoms after exposure to liquid phenol-formaldehyde resin, the other after exposure to garlic-like odor of phosphine (57). The term “behavioral sensitization to odorant” was suggested to describe such patients.

Several researchers have noted overlaps between symptoms reported in sick building syndrome outbreaks and those reported in cases of “multiple chemical sensitivities” (MCS) (28), raising the question whether MCS is an odor-triggered syndrome in some cases. The EPA-Waterside Mall sick building syndrome outbreak may be an example of a cluster of cases of odor-related MCS overlapping symptomatically with the sick building syndrome, in light of the reported exacerbation of symptoms associated with a distinctive odorant (4-phenyl cyclohexene) contained in the carpet glue which was temporally associated with many of the cases (58). The precise role of odorants in MCS is not yet clear, as some patients complain of recurrent symptoms that may appear despite lack of awareness of any odor. No evidence of hyposcopic odor thresholds has been observed to date in patients with MCS (59).

**Perception of Odorant Intensity**

Exposure to odorants produces complex sensory responses that include reception, transduction, sensations and assessment (60). Repeated exposure may result in a shift in sensitivity toward increased or decreased apparent sensitivity. For example, a study of Elizabeth, New Jersey, where environmental odor pollution was particularly common, found that decreased sensitivity with repeated exposure may occur: eugenol (clove) odors were not detected by 14% of the surveyed population, compared with only 1% of New Brunswick residents (13). Indoor air adaptation is also likely to occur, resulting in attenuation of complaints even with continued exposure (61). Ethyl mercapton is subject to rapid adaptation (62) reducing its warning properties over time when used as an LP gas odorizer.

**Asthma**

Many people with asthma identify odorants that specifically worsen their asthma. The types of odorants associated with worsening of asthma include flowers (63), insecticide, perfumes, household cleaners, cooking, cigarettes, auto exhaust, paint vapors, and body odor (64). As early as 1698, Sir John Floyer, in *A Treatise of the Asthma*, noted that strong smells such as extinguished candles or those associated with certain occupations, such as soap making, wine fermenting, or fumes of quicksilver, are harmful to those with asthma (65).

In a study of odorants and asthma, four patients were evaluated by exposure challenge with cologne and perfume, which showed immediate pulmonary function decline (FEV1) of between 18 and 58% below baseline. Pretreatment with atropine or metaproterenol prevented the decline in three of the four, while cromolyn blocked the decline in one patient (23). A survey of 30 hospitalized asthma patients and 30 clinic asthma patients was also reported. Twenty-three reported severe asthma attacks following odorant exposure requiring emergency department visit, and nine had to be hospitalized after such exposures. Odors reported to be associated with asthma exacerbations are shown in Figure 3.

The mechanism of odorant-associated asthma is not clear. Some asthmatic patients have asthma exacerbated by odorants, suggesting that perception of the odorant as odorant is not necessary to trigger the asthma. Some have suggested a psychological mechanism (66). It is often difficult to distinguish whether it is the odorant, free of the potentially allergenic material, or the allergen, free of the odorant, that causes the exacerbation.

**Cancer Risk from Indoor Odorants**

It is estimated that the indoor air exposure to the common odorant air freshener and constituent of moth balls, para-dichlorobenzene, results in a population-based risk of 83 cancer deaths per million, a risk due to VOCs that is exceeded only by benzene and chloroform (4). Other indoor odors that are likely or known human carcinogens include benzene, chloroform, formaldehyde, and most significantly, ETS.

**Interaction Between Odor and Irritation**

In view of the close association of the trigeminal nerve and the olfactory nerve with stimulation by inhaled vapors, there is thought to be likely interaction. Cain and Murphy (40) found a strong mutual interaction between pungency and odor, occurring without attenuation even when the irritating agent enters one nostril and the odorant the other.
Conclusions

"People assess the quality of the air indoors primarily on the basis of its odor, and on their perception of associated health risk" (17). The major current contributors to indoor odors are human occupant odors (body odor), ETS, volatile building materials, bio-odorants (particularly mold and animal-derived materials), air fresheners, deodorants, and perfumes. These are most often present as complex mixtures, making measurement of the total odorant problem difficult. Theolf or decipol unit may be a useful method to assess the overall amount and significance of complex chemical and biological odorants in indoor air. The standard regulatory approach, focusing on individual constituents or chemicals, is not likely to be successful in adequately controlling odorants in indoor air. Besides the current approach of setting minimum ventilation standards to prevent health effects due to indoor air pollution, a standard based on the olf or decipol unit might be more efficacious as well as simpler to measure. As buildings have become tighter, increasing attention will be needed to these sources of intentional and accidental odor to prevent the perception of danger inherent in malodors. New methods will be needed to reduce odor pollution, including eliminating indoor smoking, prohibitions against wearing loud perfumes, avoiding the use of odorant organic-solvent-based pesticide applications, preventing the use of malodorous building materials, and careful siting of outdoor air intakes to avoid reentrainment of outdoor air pollution. Future regulatory approaches may target sources other than ETS: e.g., there is a recent legislative initiative in California to encapsulate perfumed samples in magazines to prevent incidental exposure to asthmatics that may trigger their attacks.

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