The Effects of Air Pollutants and Irritants on the Upper Airway

Dennis Shusterman

Division of Occupational and Environmental Medicine, University of California, San Francisco, California

The nose and upper airway play a sentinel role in the respiratory tract, alerting an individual to the qualities of the inspired atmosphere. The upper airway also clears contaminants from the inspired airstream and physically conditions inspired air before its entry into the lower respiratory tract. Given these anatomical and functional considerations, the nose may be the initial—or even prime—target of air pollutants. This article reviews the functional anatomy of the upper airway in humans, its vulnerabilities to various classes of air contaminants, and the relationship between chemical irritation and allergic inflammation in the upper airway.

Keywords: air pollution; irritation; occupation; olfaction; upper airway

Air pollutants can contribute to the pathogenesis of upper airway conditions, including rhinitis, sinusitis, sinonasal cancer, olfactory dysfunction, and otitis media. The responses to air pollutants and allergens are not mutually exclusive, and, in fact, can influence one another, as discussed subsequently here.

FUNCTIONAL ANATOMY AND DOSIMETRY OF THE UPPER RESPIRATORY TRACT

The nasal cavity is lined by three main epithelial types: squamous, respiratory, and olfactory. The anterior nares (“nasal vestibule”) is invested with squamous epithelium, which transitions, beyond the tip of the inferior turbinate, into respiratory epithelium (1). The respiratory epithelium is pseudostratified in architecture, and includes basal cells, columnar cells (ciliated and nonciliated), and goblet cells. Serous and mucinous glands are located in the submucosal, and contribute to the composition of nasal mucus.

The superior portion of the nasal cavity houses the olfactory epithelium (peripheral portion of cranial nerve I). Branches of the trigeminal nerve (cranial nerve V) invest the nasal and oral cavities, and provide for mechanical, thermal, and chemical (irritant) sensation (Figure 1). Although mediated by separate cranial nerves, olfaction and trigeminal chemoreception together provide an integrated sensory impression of ambient air. It is not unusual, for example, for an individual to report smelling a “pungent odor,” and in doing so combine two different streams of neural information. The oropharynx and hypopharynx and also receive innervation from the glossopharyngeal (cranial nerve IX) and, to a lesser extent, vagal (cranial nerve X) nerves, which participate in upper airway irritant reflexes. The boundary between the upper and lower airway is at the level of the glottis (i.e., vocal folds).

The surface area of the nasal cavity is augmented by the architecture of the nasal turbinates, thereby enhancing the functions of filtration and air conditioning. Underlying the mucosal surface are extensive vascular beds, which provide substrate for both heat and water transfer. These vessels are reactive to various neurohumoral stimuli, and are thereby responsible, to a large degree, for acute changes in upper airway patency (2).

Large (i.e., >10-μm diameter) inspired particles tend to interact with the mucosa through the process of impaction (Figure 2). Once trapped in nasal mucus, these particles are transported posteriorly to the nasopharynx via the mucociliary blanket, and from there are either swallowed or expectorated. Gaseous/vapor-phase air pollutants can also be cleared (“scrubbed”) from inspired air, depending upon a number of factors. Chief among these are water solubility and chemical reactivity (Figure 3). Highly water-soluble and reactive irritants (such as chlorine, ammonia, sulfur dioxide, and formaldehyde) readily dissolve in mucous membrane water and quickly interact with the nose’s specialized sensory structures. These airborne irritants are considered to have good “warning properties” because of their immediate sensory impact.

Another factor influencing the clearance and fate of inspired contaminants is mucosal metabolism (3, 4). These include phase I (e.g., cytochrome P450, carboxylesterase, and aldehyde dehydrogenase) and phase II (e.g., glutathione transferase). Phase I metabolism may render inspired contaminants either more or less toxic, depending upon the specific substrate and enzyme involved. Phase II enzymes, on the other hand, detoxify exclusively.

Air pollutants vary substantially in their relative odorant and irritant potencies, with one modality at times overshadowing the other (5, 6). Exposure duration can also be an important variable in both olfaction and trigeminal chemoreception. In general, olfactory sensations tend to fade (i.e., adapt) with continued exposure, whereas trigeminal irritation often builds with time (7–9). Respiratory reflexes triggered by irritant exposure in the upper airway include rhinorrhea, nasal obstruction, sneezing, coughing, and laryngospasm (10–12). The larynx can also serve as a target in a syndrome involving paradoxical adduction of the cords (folds) during inspiration (“vocal cord dysfunction” [VCD]). A variant of the latter, so-called “irritant-associated VCD,” involves triggering by inspired chemicals, and can mimic occupational asthma (13).

PATHOPHYSIOLOGY OF THE UPPER RESPIRATORY TRACT

The pathophysiologic mechanisms involved in allergic rhinitis are well known. Briefly, mucosal mast cells with antigen-specific IgE bound to surface (FcεRI) receptors are activated upon contact with a relevant allergen. Acutely, histamine, sulfidopeptide leukotrienes, prostaglandins, and other vasoactive mediators are released, resulting in itching, sneezing, nasal secretion, and vascular congestion. In addition to the acute response, allergic reactions may give rise to late-phase rhinitis symptoms, manifested over hours, as well as tissue inflammation, which may last for days.

Upper airway “irritation” can be defined variously as stimulation of mucosal nerves (“nociceptors”), reflex changes...
trigeminal nerve (so-called “neuromodulation”) (28).

The fact that some allergic mediators increase airway nerve excitability (26, 27). The latter phenomenon likely relates to the development of rhinitis may accompany—or even precede—the development of asthma. These observations have led to the coining of the term the “one airway hypothesis” (29, 30).

Rhinitis

Although beyond the scope of this review, occupational allergic rhinitis has been documented with exposure to a wide variety of natural and synthetic substances. Among these are natural rubber latex and psyllium in health care settings, flour dust in bakeries, acid anhydrides in chemical manufacturing, persulfates in hair care, and various exotic wood dusts in sawmills and furniture factories (31–37). Of note, the lists of potential sensitizers affecting the upper and lower airways (i.e., causing rhinitis and asthma) are virtually identical (38).

Besides occupational allergic rhinitis, irritant rhinitis has been reported among workers with chronic and/or episodic exposures to irritant gases, vapors, fumes, or smoke (45). This entity is analogous to irritant-induced rhinitis. Pre-existing nasal allergies, on the other hand, can intensify the response to nasal irritants (26, 27). The latter phenomenon likely relates to the fact that some allergic mediators increase airway nerve excitability (so-called “neuromodulation”) (28).

**OCCUPATIONAL AND ENVIRONMENTAL CONDITIONS OF THE UPPER AIRWAY**

Occupational and environmental exposures should be considered when investigating a variety of upper airway diagnoses. Rhinitis, sinusitis, eustachian tube dysfunction, olfactory impairment, and VCD can all derive—wholly or in part—from environmental exposures. As noted previously here, allergic and irritant inflammatory events are not mutually exclusive, and the two processes may actually interact in a given individual. There has also been increasing recognition that inflammatory events in the upper airway may affect the lower airway, and that the development of rhinitis may accompany—or even precede—the development of asthma. These observations have led to the coining of the term the “one airway hypothesis” (29, 30).

**Figure 2.** Regional deposition of particles in the upper and lower airway, by particle diameter. Adapted with permission from Reference 82.
posed to sidestream tobacco smoke, highlighting the relevance of eustachian tube dysfunction has been demonstrated in rats experimentally. Pressure imbalance leads to fluid accumulation and infection. Along with ciliastasis, obstruction and acting through mucosal swelling, can produce obstruction of the osteomeatal complex. Allergy, viral infection, and chemical irritation, associated with olfactory impairment include metals, solvents, allergic, or chemical insults. Classes of airborne chemicals associated with VCD may report intermittent triggering of symptoms by irritant chemicals (e.g., bleach or ammonia) or by strong fragrances (S. Tilles, personal communication).

Sinusitis and Otitis Media

Many occupations involving exposure to organic dusts are also associated with self-reported sinus disease. These occupations include spice workers, furriers, hemp workers, and workers in pharmaceuticals, paper recycling, textiles, farming, and vegetable pickling (51–59). Other exposures variably associated with sinusitis include ozone (O₃), car exhaust, and water-based machining fluids (60–62).

The link between irritant exposures and the development of sinusitis has been only partially investigated. Obstruction of the osteomeatal complex, with resultant impairment of pressure equalization and compromised sinus drainage, may play a part in this process. Allergy, viral infection, and chemical irritation, acting through mucosal swelling, can produce obstruction of the osteomeatal complex. Along with ciliastasis, obstruction and pressure imbalance leads to fluid accumulation and infection. It is well established that young children exposed to second-hand tobacco smoke are at increased risk of developing otitis media with effusion (63). Similar to sinusitis, the pathogenesis of otitis media may involve irritant-related ostial (i.e., eustachian tube) dysfunction and ciliastasis (64). Experimentally, eustachian tube dysfunction has been demonstrated in rats exposed to sidestream tobacco smoke, highlighting the relevance of this pathogenic mechanism (65).

Olfactory Dysfunction

Olfaction is important for normal appetite, safety (e.g., detection of smoke or spoiled food), and social communication. Olfactory impairment can result from infectious, traumatic, allergic, or chemical insults. Classes of airborne chemicals associated with olfactory impairment include metals, solvents, irritant gases, and alkaline dusts (66, 67). Workers with significantly impaired olfaction may, under some circumstances, be denied medical clearance for use of air-purifying respirators in a chemical exposure environment, because awareness of respirator failure is enhanced by an intact sense of smell.

Chemically induced olfactory impairment can involve quantitative deficits, qualitative deficits, or both. Quantitatively, one speaks of hyposmia (in the case of reduced olfactory acuity) or anosmia (in its complete absence). Qualitatively, dysosmia refers to a distorted sense of smell, and phantosmia to olfactory sensations in the absence of odorant exposure (68). Because qualitative impairment (e.g., of odor identification) correlates broadly with quantitative impairment, highly portable qualitative screening tests, such as the University of Pennsylvania Smell Identification Test, are potentially useful in field studies of workers exposed to irritating chemicals (69). In the clinical setting, the alcohol sniff test is rapid, and has been shown to have good predictive power vis-à-vis more sophisticated odor threshold testing (70).

VCD

As noted previously here, VCD can masquerade as asthma, producing episodic dyspnea, globus sensation, cough, upper chest tightness, and noisy (stridorous) respiration. The variant of VCD in which the onset of disease follows an irritant exposure (i.e., irritant-associated VCD) has been documented with a variety of exposures. These have included chlorine gas, sodium metabisulfate dust, alkaline (e.g., WTC) dust, and vapors from disinfectant or sterilant chemicals (48, 71–73). Anecdotal data suggest that even absent an irritant-related onset, patients with VCD may report intermittent triggering of symptoms by irritant chemicals (e.g., bleach or ammonia) or by strong fragrances (S. Tilles, personal communication).

ENVIRONMENTAL EXPOSURES

Ambient Air Pollutants

Ambient (outdoor) air pollutants derive from a variety of sources, including internal combustion engines, electrical power generation, industrial operations, residential fireplaces and woodstoves, tire wear, and natural weathering of geological materials. Six specific pollutants—nitrogen oxides, sulfur dioxide, O₃, particulate matter, carbon monoxide, and lead—are considered “criteria air pollutants” by the U.S. Environmental Protection Agency, and are subject to intensive monitoring and area-wide compliance measures. Of these, all but the last two are respiratory tract irritants (74). So-called “toxic air contaminants” include a variety of compounds that either have serious irritant potential or for which there is evidence of carcinogenicity or other specific target organ toxicity. In general, control strategies for toxic air contaminants rely more on source modeling and permitting than on routine environmental monitoring.

Exposures to photochemical oxidants, such as O₃ and peroxyacetyl nitrate, can produce histologic changes in the nasal mucosa (75). For example, young adults from rural Mexico who spent 2 weeks in (highly-polluted) Mexico City exhibited inflammatory changes in their nasal epithelia (76). Both children and adults exposed to air pollution in Mexico City, when compared with their rural counterparts, showed evidence of DNA damage in exfoliated nasal cells (77).

Indoor Air Pollutants

Along with headache, drowsiness, and skin complaints, sensory irritation is a leading symptom constellation in so-called “non-specific building-related illness” or “sick building syndrome” (78). Irritants in indoor air can include combustion products (second-hand tobacco smoke, exhaust from malfunctioning combustion appliances, retrained vehicular exhaust), as well as...
as volatile organic compounds (VOCs) (from building materials, interior furnishings, and cleaning products). Additional VOCs can derive from microbial growth (“microbial VOCs”) (79). Both nitrogen oxides and O₃ can be generated indoors by the operation of gas stoves or electrical equipment, respectively. Secondary irritants can be formed indoors from chemical reactions between O₃ or nitrogen oxides and selected VOCs (e.g., terpenes, as found in many “green” cleaning products) (80). One of these reaction products is formaldehyde, which is often associated with sensory irritation.

CONCLUSIONS
The nose, paranasal sinuses, eustachian tubes, and larynx are upper airway structures vulnerable to environmental insult. Depending upon their physical and chemical properties, air pollutants may, in fact, take their primary toll on the upper airway. Awareness of the spectrum of upper airway injury from irritant chemicals helps clinicians and risk assessors achieve a more comprehensive perspective on air pollutant health effects.

Author Disclosure: D.S. was a consultant for Thomas & Wan, LLP ($1,001–$5,000) and received grant support from GlaxoSmithKline ($50,001–$100,000) and FAMHI (more than $100,001). He receives royalties from Informa Healthcare (up to $1,000).

References