The Effects of Air Pollutants and Irritants on the Upper Airway

Dennis Shusterman[1]

[1]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 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 mucous, 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 ($F_{C\varepsilon}$) 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

(*Received in original form March 13, 2010; accepted in final form July 14, 2010*)

Correspondence and requests for reprints should be addressed to Dennis Shusterman, M.D., M.P.H., Division of Occupational and Environmental Medicine, University of California, San Francisco, Box 0843, San Francisco, CA 94143-0843. E-mail: dshusterman@sfghoem.ucsf.edu

Proc Am Thorac Soc Vol 8. pp 101–105, 2011
DOI: 10.1513/pats.201003-027RN
Internet address: www.atsjournals.org

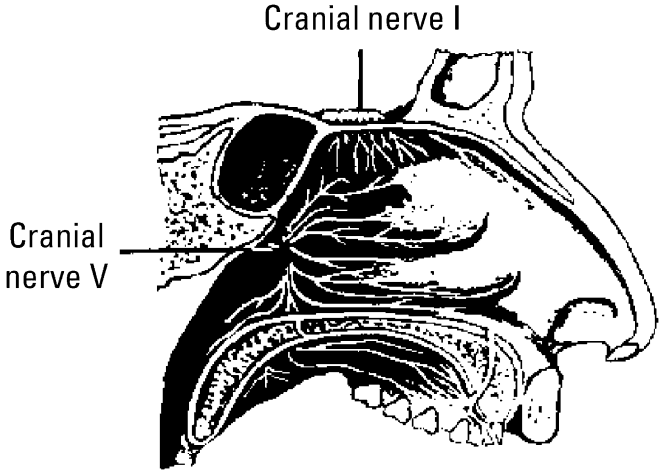


Figure 1. Innervation of the nasal cavity: cranial nerve I = olfactory nerve; cranial nerve V = trigeminal nerve. Reproduced with permission from Reference 81.

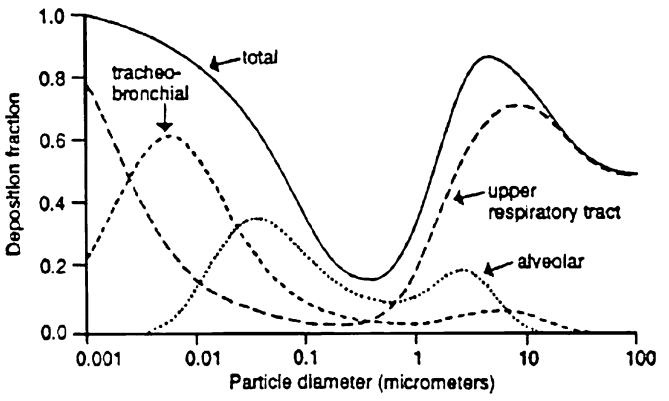


Figure 2. Regional deposition of particles in the upper and lower airway, by particle diameter. Adapted with permission from Reference 82.

triggered by nerve stimulation, chemically induced tissue damage, or some combination of the above (14). Airborne chemicals can trigger an array of irritant receptors located on airway afferent nerves (generally C and Aδ fibers) (15–17). Until recently, these structures were considered to be exclusively "free nerve endings," although the discovery of specialized "solitary chemoreceptor cells" in other species has occasioned a search for these structures in humans as well (18).

Irritation in the trigeminal distribution (eye, nose, and throat) has been termed "sensory irritation." Both animal and human study models exist for this phenomenon. Rodents exposed to sensory irritants show a characteristic slowing of respiration, with the concentration (or "dose") producing a 50% reduction in respiratory rate being termed the "RD_{50}" (19). The relative potency of airborne chemicals in eliciting respiratory slowing in rodents also predicts their potency in eliciting human sensory irritation (20). Furthermore, potencies in eliciting ocular and nasal irritation (both trigeminally innervated structures) are closely correlated in human ("psychophysical") studies (21). Finally, both ocular and nasal irritant potencies can be modeled based upon the physicochemical properties of the chemicals in question (22).

Although allergy and irritation are normally thought of as distinct processes, there is considerable interaction between the two. Exposure to selected air pollutants (i.e., diesel exhaust and second-hand tobacco smoke) can reinforce allergic sensitization and intensify allergic reactions (23–25). 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).

Rhinitis

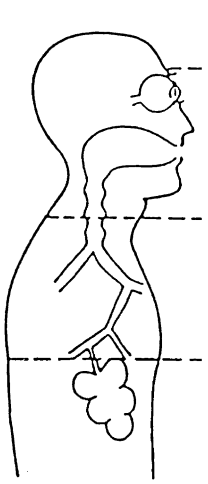
Although beyond the scope of this review, occupational allergic rhinitis has been documented with exposure to a wide variety of natural and synthetic substances. Among these are natural rubber latex and psyllium in health care settings, flour dust in bakeries, acid anhydrides in chemical manufacturing, 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 smokes (e.g., pulp mill workers exposed to chlorine gas) (39). Chronic exposure to hexavalent chromium from welding fumes or metal plating operations can result in nasal erosions and even nasal septal perforation (40). Sinonasal cancer has also been linked to a variety of occupations, including those involving chronic exposures to wood dust, formaldehyde, nickel salts, as well as leather dust, welding fumes, and arsenic (41–44).

The acronym RUDS ("reactive upper airways dysfunction syndrome") was coined to describe chronic rhinitis occurring after a one-time, high-level exposure to an irritant gas, vapor, dust, or smoke (45). This entity is analogous to irritant-induced asthma/reactive airways dysfunction syndrome (RADS) (46). However, unlike the RADS case definition, the RUDS diagnosis does not involve a specific physiologic test (e.g., the methacholine challenge in RADS), placing a predominant emphasis on occupational history taking.

Relevant to the RUDS diagnosis, unexpectedly high rates of rhinitis, sinusitis, gastroesophageal reflux disease, and VCD have been documented among workers and residents exposed to smoke and dust from the World Trade Center (WTC) disaster (47, 48). Along with bronchial hyperreactivity, these upper airway conditions may have derived from the caustic nature of WTC dust (pH 9–10) (49). Long-term follow-up of these occupationally and environmentally exposed individuals is ongoing in a number of different settings.

Idiopathic nonallergic rhinitis is also referred to as "vasomotor rhinitis," "nonallergic, noninfectious perennial rhinitis," or "noninfectious, nonallergic rhinitis." This disorder has, as a defining characteristic, nonspecific hyperreactivity to physical



Water Solubility	Initial Level of Impact	Compounds
High	Eyes	Aldehydes
	Nose	Ammonia
	Pharynx	Chlorine
	Larynx	Sulfur Dioxide
Medium	Trachea	Ozone
	Bronchi	
Low	Bronchioles	Nitrogen Dioxide
	Alveoli	Phosgene

Source: USDHHS, Surgeon General's Office: The Health Consequences of Involuntary Smoking. 1986

Figure 3. Regional deposition of gases and vapors in the upper and lower airway, by water solubility.

and/or chemical stimuli. A substantial subset (~40%) of subjects with *allergic* rhinitis also reports prominent reactivity to nonallergic stimuli (50). For individuals with nonallergic rhinitis, problematic exposures include workplace irritants and odorants, as well as cold or windy weather, work in "cold rooms" (e.g., in biotechnology), or excessively dry air (e.g., in "clean rooms" or aircraft environments).

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 (O_3), 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 irritant 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 metabisufate 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, O_3, 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 O_3 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 "nonspecific 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, reintrained vehicular exhaust), as well

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 O_3 can be generated indoors by the operation of gas stoves or electrical equipment, respectively. Secondary irritants can be formed indoors from chemical reactions between O_3 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 FAMRI (more than $100,001). He receives royalties from Informa Healthcare (up to $1,000).

References

1. Baroody FM. Functional anatomy of the upper airway in humans. In: Morris JB, Shusterman DJ, editors. Toxicology of the nose and upper airways. New York: Informa Healthcare; 2010. pp. 18–44.
2. Druce HM. Nasal blood flow. *Ann Allergy* 1993;71:288–291.
3. Ding X, Dahl AR. Olfactory mucosa: composition, enzymatic localization and metabolism. In: RL Doty, editor. Handbook of olfaction and gustation, 2nd ed. New York: Marcel Dekker; 2003. pp. 51–73.
4. Morris JB, Shusterman DJ. Nasal enzymology and its relevance to nasal toxicity and disease pathogenesis. In: Morris JB, Shusterman DJ, editors. Toxicology of the nose and upper airways. New York: Informa Healthcare; 2010. pp. 82–97.
5. Amoore JE, Hautala E. Odor as an aid to chemical safety: odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. *J Appl Toxicol* 1983;3:272–290.
6. Shusterman D. Odor-associated health complaints: competing explanatory models. *Chem Senses* 2001;26:339–343.
7. Dalton P. Psychophysical and behavioral characteristics of olfactory adaptation. *Chem Senses* 2000;25:487–492.
8. Wise PM, Zhao K, Wysocki CJ. Dynamics of nasal chemesthesis. *Ann N Y Acad Sci* 2009;1170:206–214.
9. Shusterman D, Matovinovic E, Salmon A. Does Haber's law apply to human sensory irritation? *Inhal Toxicol* 2006;18:457–471.
10. Widdicombe JG. Nasal pathophysiology. *Respir Med* 1990;84(Suppl A): 3–9; discussion 9–10.
11. Tai CF, Baraniuk JN. Upper airway neurogenic mechanisms. *Curr Opin Allergy Clin Immunol* 2002;2:11–19.
12. Raphael GD, Baraniuk JN, Kaliner MA. How and why the nose runs. *J Allergy Clin Immunol* 1991;87:457–467.
13. Perkner JJ, Fennelly KP, Balkissoon R, Bartelson BB, Ruttenber AJ, Wood RP II, Newman LS. Irritant-associated vocal cord dysfunction. *J Occup Environ Med* 1998;40:136–143.
14. Green BG, Mason JR, Kare MR. Preface. In: Green BG, Mason JR, Kare MR, editors. Chemical senses, Vol 2: irritation. New York: Marcel Dekker; 1990. pp. v–vii.
15. Caterina MJ, Schumacher MA, Tominaga M, Rosen TA, Levine JD, Julius D. The capsaicin receptor: a heat-activated ion channel in the pain pathway. *Nature* 1997;389:816–824.
16. Julius D, Basbaum AI. Molecular mechanisms of nociception. *Nature* 2001;413:203–210.
17. Bessac BF, Sivula M, von Hehn CA, Escalera J, Cohn L, Jordt SE. TRPA1 is a major oxidant sensor in murine airway sensory neurons. *J Clin Invest* 2008;118:1899–1910.
18. Silver WL, Finger TE. The anatomical and electrophysiological basis of peripheral nasal trigeminal chemoreception. *Ann N Y Acad Sci* 2009; 1170:202–205.
19. Alarie Y. Sensory irritation by airborne chemicals. *CRC Crit Rev Toxicol* 1973;2:299–363.
20. Kuwabara Y, Alexeeff GV, Broadwin R, Salmon AG. Evaluation and application of the RD50 for determining acceptable exposure levels of airborne sensory irritants for the general public. *Environ Health Perspect* 2007;115:1609–1616.
21. Doty RL, Cometto-Muñiz JE, Jalowayski AA, Dalton P, Kendal-Reed M, Hodgson M. Assessment of upper respiratory tract and ocular irritative effects of volatile chemicals in humans. *Crit Rev Toxicol* 2004;34:85–142.
22. Abraham MH, Sánchez-Moreno R, Cometto-Muñiz JE, Cain WS. A quantitative structure activity analysis on the relative sensitivity of the olfactory and the nasal trigeminal chemosensory systems. *Chem Senses* 2007;32:711–719.
23. Diaz-Sanchez D, Garcia MP, Wang M, Jyrala M, Saxon A. Nasal challenge with diesel exhaust particles can induce sensitization to a neoallergen in the human mucosa. *J Allergy Clin Immunol* 1999;104:1183–1188.
24. Diaz-Sanchez D, Penichet-Garcia M, Saxon A. Diesel exhaust particles directly induce activated mast cells to degranulate and increase histamine levels and symptom severity. *J Allergy Clin Immunol* 2000;106:1140–1146.
25. Diaz-Sanchez D, Rumold R, Gong H Jr. Challenge with environmental tobacco smoke exacerbates allergic airway disease in human beings. *J Allergy Clin Immunol* 2006;118:441–446.
26. Shusterman D, Murpy M-A, Balmes J. Influence of age, gender and allergy status on nasal reactivity to inhaled chlorine. *Inhal Toxicol* 2003a;15:1179–1189.
27. Shusterman D, Murphy M-A, Balmes J. Differences in nasal irritant sensitivity by age, gender, and allergic rhinitis status. *Int Arch Occup Environ Health* 2003b;76:577–583.
28. Carr MJ, Undem BJ. Inflammation-induced plasticity of the afferent innervation of the airways. *Environ Health Perspect* 2001;109:567–571.
29. Corren J, Kachru R. Relationship between nonallergic upper airway disease and asthma. *Clin Allergy Immunol* 2007;19:101–114.
30. Corren J. The connection between allergic rhinitis and bronchial asthma. *Curr Opin Pulm Med* 2007;13:13–18.
31. Moneret-Vautrin DA, Debra JC, Kohler C, Stringini R, Kanny G, Guillaumot A, Buthmann D. *et al.* Occupational rhinitis and asthma to latex. *Rhinology* 1994;32:198–202.
32. Schwartz HJ, Arnold JL, Strohl KP. Occupational allergic rhinitis reaction to psyllium. *J Occup Med* 1989;31:624–626.
33. Brisman J, Toren K, Lillienberg L, Karlsson G, Ahlstedt S. Nasal symptoms and indices of nasal inflammation in flour-dust-exposed bakers. *Int Arch Occup Environ Health* 1998;71:525–532.
34. Bernstein DI, Patterson R, Zeiss CR. Clinical and immunologic evaluation of trimellitic anhydride– and phthalic anhydride–exposed workers using a questionnaire with comparative analysis of enzyme-linked immunosorbent and radioimmunoassay studies. *J Allergy Clin Immunol* 1982;69:311–318.
35. Schwartz HJ, Arnold JL, Strohl KP. Occupational allergic rhinitis in the hair care industry: reactions to permanent wave solutions. *J Occup Med* 1990;32:473–475.
36. Aguwa EN, Okeke TA, Asuzu MC. The prevalence of occupational asthma and rhinitis among woodworkers in south-eastern Nigeria. *Tanzan Health Res Bull* 2007;9:52–55.
37. Eire MA, Pineda F, Losada SV, de la Cuesta CG, Villalva MM. Occupational rhinitis and asthma due to cedroarana (*Cedrelinga catenaeformis* Ducke) wood dust allergy. *J Investig Allergol Clin Immunol* 2006;16:385–387.
38. Moscato G, Vandenplas O, Gerth Van Wijk R, Malo JL, Quirce S, Walusiak J, Castano R, De Groot H, Folletti I, Gautrin D, *et al.* Occupational rhinitis. *Allergy* 2008;63:969–980.
39. Leroyer C, Malo JL, Girard D, Dufour JG, Gautrin D. Chronic rhinitis in workers at risk of reactive airways dysfunction syndrome due to exposure to chlorine. *Occup Environ Med* 1999;56:334–338.
40. Lin SC, Tai CC, Chan CC, Wang JD. Nasal septum lesions caused by chromium exposure among chromium electroplating workers. *Am J Ind Med* 1994;26:221–228.
41. Comba P, Battista G, Belli S, de Capua B, Merler E, Orsi D, Rodella S, Vindigni C, Axelson O. A case-control study of cancer of the nose and paranasal sinuses and occupational exposures. *Am J Ind Med* 1992;22:511–520.
42. d'Errico A, Pasian S, Baratti A, *et al.* A case-control study on occupational risk factors for sino-nasal cancer. *Occup Environ Med* 2009;66:448–455.
43. Demers PA, Kogevinas M, Boffetta P, Leclerc A, Luce, D, Gerin, M, Battista G, Belli S, Bolm-Audorf U, Brinton LA, *et al.* Wood dust and sino-nasal cancer: pooled reanalysis of twelve case-control studies. *Am J Ind Med* 1995;28:151–166.

44. Grimsrud TK, Peto J. Persisting risk of nickel related lung cancer and nasal cancer among Clydach refiners. *Occup Environ Med* 2006;63:365–366.
45. Meggs WJ. RADS and RUDS—the toxic induction of asthma and rhinitis. *J Toxicol Clin Toxicol* 1994;32:487–501.
46. Brooks SM, Weiss MA, Bernstein IL. Reactive airways dysfunction syndrome (RADS): persistent asthma syndrome after high level irritant exposures. *Chest* 1985;88:376–384.
47. Banauch GI, Dhala A, Alleyne D, Alva R, Santhyadka G, Krasko A, Weiden M, Kelly KJ, Prezant DJ. Bronchial hyperreactivity and other inhalation lung injuries in rescue/recovery workers after the World Trade Center collapse. *Crit Care Med* 2005;33(1 Suppl):S102–S106.
48. de la Hoz RE, Shohet MR, Bienenfeld LA, Afilaka AA, Levin SM, Herbert R. Vocal cord dysfunction in former World Trade Center (WTC) rescue and recovery workers and volunteers. *Am J Ind Med* 2008;51:161–165.
49. McGee JK, Chen LC, Cohen MD, Chee GR, Prophete CM, Haykal-Coates N, Wasson SJ, Conner TL, Costa DL, Gavett SH. Chemical analysis of World Trade Center fine particulate matter for use in toxicologic assessment. *Environ Health Perspect* 2003;111:972–980.
50. Shusterman D, Murphy MA. Nasal hyperreactivity in allergic and non-allergic rhinitis: a potential risk factor for non-specific building-related illness. *Indoor Air* 2007;17:328–333.
51. Zuskin E, Kanceljak B, Pokrajac D, Schachter EN, Witek TJ Jr. Respiratory symptoms and lung function in hemp workers. *Br J Ind Med* 1990;47:627–632.
52. Zuskin E, Mustajbegovic J, Schachter EN, Kanceljak B, Godnic-Cvar J, Sitar-Srebocan V. Respiratory symptoms and lung function in wool textile workers. *Am J Ind Med* 1995;27:845–857.
53. Zuskin E, Mustajbegovic J, Schachter EN, Kanceljak B, Kern J, Macan J, Ebling Z. Respiratory function and immunological status in paper-recycling workers. *J Occup Environ Med* 1998;40:986–993.
54. Zuskin E, Mustajbegovic J, Schachter EN, Kern J, Budak A, Godnic-Cvar J. Respiratory findings in synthetic textile workers. *Am J Ind Med* 1998;33:263–273.
55. Zuskin E, Mustajbegovic J, Schachter EN, Kern J, Deckovic-Vukres V, Pucarin-Cvetkovic J, Nola-Premec IA. Respiratory findings in pharmaceutical workers. *Am J Ind Med* 2004;46:472–479.
56. Zuskin E, Mustajbegovic J, Schachter EN, Rienzi N. Respiratory symptoms and ventilatory capacity in workers in a vegetable pickling and mustard production facility. *Int Arch Occup Environ Health* 1993; 64:457–461.
57. Zuskin E, Skuric Z, Kanceljak B, Pokrajac D, Schachter EN, Witek TJ. Respiratory findings in spice factory workers. *Arch Environ Health* 1988;43:335–339.
58. Zuskin E, Skuric Z, Kanceljak B, Pokrajac D, Schachter EN, Witek TJ Jr. Respiratory symptoms and lung function in furriers. *Am J Ind Med* 1988;14:187–196.
59. Bener A, Lestringant GG, Beshwari MM, Pasha MA. Respiratory symptoms, skin disorders and serum IgE levels in farm workers. *Allerg Immunol (Paris)* 1999;31:52–56.
60. Parks S, Paul DW. Ozone exposure: a case report and discussion. *J Okla State Med Assoc* 2000;93:48–51.
61. Bener A, Galadari I, al-Mutawa JK, al-Maskari F, Das M, Abuzeid MS. Respiratory symptoms and lung function in garage workers and taxi drivers. *J R Soc Promot Health* 1998;118:346–353.
62. Park D, Choi B, Kim S, Kwag H, Joo K, Jeong J. Exposure assessment to suggest the cause of sinusitis developed in grinding operations utilizing soluble metalworking fluids. *J Occup Health* 2005;47:319–326.
63. Etzel RA, Pattishall EN, Haley NJ, Fletcher RH, Henderson FW. Passive smoking and middle ear effusion among children in day care. *Pediatrics* 1992;90:228–232.
64. Agius AM, Wake M, Pahor AL, Smallman A. The effects of in vitro cotinine on nasal ciliary beat frequency. *Clin Otolaryngol Allied Sci* 1995;20:465–469.
65. Dubin MG, Pollock HW, Ebert CS, Berg E, Buenting JE, Prazma JP. Eustachian tube dysfunction after tobacco smoke exposure. *Otolaryngol Head Neck Surg* 2002;126:14–19.
66. Amoore JE. Effects of chemical exposure on olfaction in humans. In: Barrows CS, editor. Toxicology of the Nasal Passages. New York: Hemisphere Publishing Corp.; 1986. pp. 155–190.
67. Dalton P. Olfactory toxicity in humans and experimental animals. In: Morris JB, Shusterman DJ, editors. Toxicology of the Nose and Upper Airways. New York: Informa Healthcare; 2010. pp. 215–241.
68. Murphy C, Doty RL, Duncan HJ. Clinical disorders of olfaction. In: Doty RL, editor. Handbook of olfaction and gestation, 2nd ed. New York: Marcel Dekker; 2003. pp. 752–779.
69. Doty RL, Shaman P, Kimmelman CP, Dann MS. University of Pennsylvania Smell Identification Test: a rapid quantitative olfactory function test for the clinic. *Laryngoscope* 1984;94:176–178.
70. Davidson TM, Murphy C. Rapid clinical evaluation of anosmia: the alcohol sniff test. *Arch Otolaryngol Head Neck Surg* 1997;123:591–594.
71. Allan PF, Abouchahine S, Harvis L, Morris MJ. Progressive vocal cord dysfunction subsequent to a chlorine gas exposure. *J Voice* 2006;20: 291–296.
72. Steiner M, Scaife A, Semple S, Hulks G, Ayres JG. Sodium metabisulphite induced airways disease in the fishing and fish-processing industry. *Occup Med (Lond)* 2008;58:545–550.
73. Tonini S, Dellabianca A, Costa CM, Lanfranco A, Scafa F, Candura SM. Irritant vocal cord dysfunction and occupational bronchial asthma: differential diagnosis in a health care worker. *Int J Occup Med Environ Health* 2010;22:401–406.
74. Suh HH, Bahadori T, Vallarino J, Spengler JD. Criteria air pollutants and toxic air pollutants. *Environ Health Perspect* 2000;108: 625–633.
75. Fortoul TI, Falcon-Rodriguez CI, Rodriguez-Lara V, Lopez-Valdez N, Montano LF, Avila-Casado MC, Mussali-Galante P. Biomarkers of nasal toxicity in humans. In: Morris JB, Shusterman DJ, editors. Toxicology of the nose and upper airways. New York: Informa Healthcare; 2010. pp. 167–173.
76. Calderon-Garcidueñas L, Rodriguez-Alcaraz A, Garcia R, Sanchez G, Barragan G, Camacho R, Ramirez L. Human nasal mucosal changes after exposure to urban pollution. *Environ Health Perspect* 1994;102: 1074–1080.
77. Calderon-Garciduenas L, Osnaya-Brizuela N, Ramirez-Martinez L, Villarreal-Calderon A. DNA strand breaks in human nasal respiratory epithelium are induced upon exposure to urban pollution. *Environ Health Perspect* 1996;104:160–168.
78. Cometto-Muniz JE, Cain WS. Sensory irritation: relation to indoor air pollution. *Ann N Y Acad Sci* 1992;641:137–151.
79. Korpi A, Jarnberg J, Pasanen AL. Microbial volatile organic compounds. *Crit Rev Toxicol* 2009;39:139–193.
80. Wolkoff P, Clausen PA, Larsen K, Hammer M, Larsen ST, Nielsen GD. Acute airway effects of ozone-initiated d-limonene chemistry: importance of gaseous products. *Toxicol Lett* 2008;181:171–176.
81. Shusterman D. Review of the upper airway, including olfaction, as mediator of symptoms. *Environ Health Perspect* 2002;110 (suppl 4): 649–653.
82. Snipes MB. Biokinetics of inhaled radionuclides. In Raabe OG, ed. Internal radiation dosimetry. Madison, WI: Medical Physics Publishing, 1994. p. 184.