Normal functioning of the olfactory system is a prerequisite for the detection of several chemical environmental hazards (e.g., spoiled foods, leaking natural gas, smoke and various airborne pollutants), and for the full appreciation of foods, beverages, flowers, perfumes, spices, the seashore, the mountains, and the seasons of the year. Distortions or loss of smell function can adversely influence food preferences, food intake, and appetite, and in some cases can lead to significant psychological depression. It is thus no wonder that dysfunction of olfaction is of considerable concern to persons who experience it, particularly those dependent on this sense for their livelihood or safety (e.g., cooks, homemakers, plumbers, fire fighters, perfumers, fragrance sales persons, wine merchants, coffee or tea tasters, food and beverage distributors, and employees of numerous chemical, gas, and public works industries).

Although smell dysfunction secondary to toxic exposure is generally less common than smell dysfunction caused by a number of other causes (e.g., upper respiratory infections, head trauma, chronic rhinitis or rhinosinusitis), it nonetheless exists. In addition to directly damaging the olfactory mucosa, some toxins may, in fact, induce upper respiratory inflammatory responses or infections that produce such damage, as well as enter the central nervous system (CNS) and cause damage to CNS structures. Olfactory loss can occur as a result of exposure to toxins in general air pollution and in workplace situations, where litigation becomes a consideration. Most cases of toxin-related olfactory loss do not get referred to specialized centers such as ours for evaluation. In fact, smell function is rarely
assessed quantitatively by local medical personnel, despite the availability of accurate, easy-to-use, and inexpensive tests for this purpose. Unfortunately, there continues to be a paucity of quantitative research investigating toxin-related effects on the sense of smell, and most reports of such effects are mainly anecdotal in nature.

In this article, we first describe basic elements of nasal airflow and the peripheral anatomy of the human olfactory system.* We then discuss common methods for quantitatively evaluating smell function, and subsequently present an overview of the types of toxic agents that reportedly alter such function. Included are studies of toxic metals (e.g., cadmium, mercury), irritant gases (e.g., SO₂, formaldehyde), and solvents (e.g., acetone). Although the emphasis of the review is on humans, a listing of toxic agents known to damage the olfactory epithelia of rodents is provided, and data from animal studies are discussed when they relate to findings from human studies.

PERIPHERAL Olfactory SYSTEM ANATOMY

Most toxic agents adversely influence olfaction by directly damaging the olfactory neuroepithelium, which is located in the upper recesses of the nasal chambers, lining the cribriform plate and sectors of the superior turbinate, superior septum, and middle turbinate (Fig. 1). Although most of this epithelium is positioned away from the main airstream and, hence, is thought to be protected to some degree from inhaled vapors, xenobiotics still readily reach this vulnerable region. As noted by Swift and Proctor, under conditions of normal resting inspiration (0.15–0.25 L/s), air passes at a vertical angle upwards through the anterior naris at a velocity of 2 to 3 meters per second. At this point, from 10% to 15% of the airstream is shunted toward the olfactory cleft. At the termination of the vestibule (i.e., the ostium internum, the most narrow and restrictive portion of the entire airway), the main airstream changes direction from vertical to horizontal. At this transition point, the airstream reaches hurricane-force velocities (12–18 m/s) before exiting the area and returning to speeds less than 4 meters per second. The highly nonlaminar (turbulent) flow that develops after the ostium internum results in increased contact with the blood swollen turbinates, thereby warming, cleansing, and humidifying the major portion of the airstream.

*In addition to the main olfactory system (cranial nerve I), the reader should be aware that other specialized neural systems are present in the nose. These include (1) trigeminal afferents responsible, for example, for the coolness of menthol vapors and irritative responses to volatile chemicals; (2) a rudimentary and nonfunctional vomeronasal organ near the base of the septum; and (3) the poorly understood nervus terminalis or terminal nerve (CN 0). CN 0, a highly conserved neural plexus that ramifies throughout the nasal epithelium, is distinguished by ganglia at nodal points and a high gonadotropin content.
Figure 1. Cross-section of the nose showing the nasal turbinates and the location of the olfactory neuroepithelium. (Copyright 2001, Richard L. Doty.)
The olfactory epithelium begins to lose its homogeneity soon after birth. Indeed, as early as the first few weeks of life, metaplastic islands of respiratory-like epithelia begin to appear within its borders, presumably as a result of insults from environmental viruses, bacteria, and toxins. These islands increase in extent and number throughout life. Surprisingly, in part because of the cumulative metaplasia and the age-related heterogeneity of the epithelium, the exact size of the olfactory epithelium in humans is still not well established, and there is suggestion that it may extend, in adults, further onto the middle turbinate than previously believed.

The mature olfactory epithelium is comprised of at least six distinct cell types (Fig. 2). The first, the bipolar sensory receptor neuron, reportedly numbers approximately 6 million in the adult, exceeding the number of receptor cells in any other sensory system except vision. The olfactory receptors are located on the ciliated dendritic ends of these cells whose axons coalesce into 30 to 50 “olfactory fila,” which are ensheathed by Schwann-like cells. The fila traverse the cribriform plate of the ethmoid bone to enter the anterior cranial fossa and collectively constitute cranial nerve I. The second cell type, the microvillar cell, is located near the surface of the epithelium and projects microvillae into the mucus. These cells, whose function is unknown, are said to number approximately 600,000 in the adult. The third cell type, the supporting or sustentacular cell, also projects microvillae into the mucus. These cells are believed to (1) insulate the receptor cells from one another, (2) contribute to and regulate the local ionic composition of the mucus, (3) deactivate odorants, and (4) aid in protecting the epithelium from damage from foreign agents. As noted in detail later in this article, the supporting cells contain several xenobiotic-metabolizing enzymes, a feature shared with the cells that line the Bowman’s glands and ducts. The latter glands provide most of the mucus in the region of the olfactory epithelium. The fifth and sixth cell types are the globose (light) basal cell and horizontal (dark) basal cell. These cells are located near the basement membrane from which the other cell types arise. It is believed that globose cells can give rise to both neurons and non-neural cells when the olfactory epithelium is damaged, expressing a rare multipotency for stem cells. Although continuous neurogenesis occurs in the basal sectors of the neuroepithelium, long-lived receptor cells have been identified, and both endogenous and exogenous factors promote receptor cell death or replenishment from the progenitor stem cells. The olfactory ensheathing cells, which form the bundles of axons that comprise the olfactory fila, play an important role in guiding regenerating axons to their bulbar targets and have unique properties useful in repair or regeneration of both central and peripheral nerves. For example, they enhance remyelination and axonal conduction in demyelinated spinal tract nerves and in severed rat sciatic nerves, exhibiting both Schwann cell-like and astrocyte-like properties.
The receptor cell cilia differ from the cilia of the respiratory epithelium in being longer and lacking dynein arms (and therefore intrinsic motility). In some cases, specialized proteins (odorant binding proteins) aid in the transport of odorants through the mucus. Approximately 1000 types of odorant receptors are now believed to exist. Most olfactory receptors appear to be linked to the stimulatory guanine nucleotide-binding protein $G_{olf}$. When stimulated, they activate the enzyme adenylyl cyclase to produce the second messenger adenosine monophosphate (cAMP) and
subsequent events related to depolarization of the cell membrane and signal propagation. In the few rodent species that have been evaluated, the olfactory receptors are topographically organized into four strip-like zones that roughly parallel the dorsal-ventral axis of the cribriform plate.\textsuperscript{109}

**METHODS OF EVALUATING OLFACTORY FUNCTION**

An astute physician of yesteryear tested the sense of smell by asking a patient to identify several crude odorants, such as coffee grounds, cloves, or perfume placed under the nose, perhaps testing one side at a time by closing the contralateral naris with a finger. This qualitative approach to smell testing, however, was unreliable, was easily faked by malingerers, and provided no information on the relative degree of dysfunction. Importantly, it often led to the wrong conclusions, because persons have difficulty accurately identifying an odor without being presented with alternatives.

Fortunately, advances in the technology of psychophysical measurement and the proliferation of easy-to-use and commercially available tests of olfactory function now make it possible for toxicologists and others to accurately and quantitatively assess the ability to smell.\textsuperscript{29} With the exception of dysosmia and phantosmia (whose diagnoses are based solely on patient report), quantitative psychophysical testing allows for the assignment of patients to specific sensory diagnostic categories. The following categories are widely accepted: Anosmia: inability to detect qualitative olfactory sensations (i.e., absence of smell function); partial anosmia: ability to perceive some, but not all, odors; hyposmia or microsmia: decreased sensitivity to odors; hyperosmia: abnormally acute smell function; dysosmia (sometimes termed cacosmia or parosmia): distorted or perverted smell perception to odor stimulation); phantosmia: a dysosmic sensation perceived in the absence of an odor stimulus (also known as olfactory hallucination); and agnosia (olfactory): inability to recognize an odor sensation, even though olfactory processing, language, and general intellectual functions are essentially intact, as in some stroke patients. Olfactory dysfunction can also be classified into bilateral or unilateral categories (sometimes termed binausal or uninasal). In most cases, bilateral test scores reflect the better functioning of the two sides of the nose. Although presbyosmia is sometimes used to describe smell loss caused by aging, this term does not distinguish between anosmia and hyposmia and implies that it is age per se, that is causing the age-related deficit.

The most popular quantitative olfactory tests are those of odor identification, discrimination, memory, and detection. Self-administered tests that use microencapsulation technology (i.e., “scratch and sniff” odorants) are the most widely used, including the 40-odor University of Pennsylvania Smell Identification Test (UPSIT; known commercially as the Smell
Identification Test [SIT]),\textsuperscript{25,29,33} the 12-odor Brief-Smell Identification Test (B-SIT; also known as the Cross-Cultural Smell Identification Test),\textsuperscript{30} the 3-odor Pocket Smell Test (PST),\textsuperscript{31} and the 12-item Odor Memory Test (OMT) (Sensonics, Inc., Haddon Heights, NJ).\textsuperscript{31} The UPSIT (which has age- and gender-based norms that allow for a determination of an individual’s percentile rank relative to peers) has been administered to over 200,000 people in Europe and North America and is available in English, Spanish, French, and German language versions (Fig. 3).\textsuperscript{25,34}

Threshold tests have also become popular for assessing olfactory function, in part because of their intuitive appeal, their commercial availability,\textsuperscript{4,26,106} and practical considerations (i.e., need for establishing at what concentration a given chemical elicits a noticeable odor). Accurate threshold testing is time consuming and more complicated than what would appear on the surface, however, even though the measurement of olfactory

![Figure 3. The four booklets of the 40-odorant University of Pennsylvania Smell Identification Test (UPSIT; commercially known as the Smell Identification Test). Each page of each 10-page booklet contains a microencapsulated odorant that is released by means of a pencil tip, and a multiple-choice question as to which of four possibilities smells most like the odorant. Forced-choice answers are recorded on columns on the last page of the test. (Courtesy of Sensonics, Inc., Haddon Heights, NJ 08035 USA. Copyright 2000, Sensonics, Inc., with permission.)](image-url)
thresholds seems straightforward and regulatory agencies and others frequently report "the threshold value" for a given chemical. Thus, there are several types of olfactory thresholds, including detection thresholds, identification thresholds, and differential thresholds. Even within a threshold class, there are a variety of procedures for presenting the stimuli and operationally defining the threshold, all of which have an effect on the final threshold value. For example, the number of trials used, the use or nonuse of forced-choice trials, the magnitude of the stimulus steps, and the nature of the dilution medium all have an effect on the threshold measure.\textsuperscript{28,31,81} Importantly, the empirically defined threshold value is a function of the human observer, being influenced by factors such as the subject's age and general health.\textsuperscript{71} Even when the number of molecules entering the nose is known, further dilution of the stimulus occurs in the nose, making it impossible to specify the exact number of molecules reaching the olfactory receptors. This number depends on such variables as the size of the sniff, the size of the nose, the size and shape of the nasal turbinates, the thickness of the mucus, and numerous other idiosyncratic parameters. Fortunately, from a practical perspective, the olfactory system is very sensitive to the first few molecules it receives, minimizing the effect of such variables on the threshold measure.

The lowest concentration of an odorant that an individual can reliably detect (usually defined as that concentration where detection is midway between chance and perfect detection) is termed his or her detection or absolute threshold. At very low concentrations, no odor quality can be discerned, only that something is present that differs from air or the comparison diluent blank or blanks. In modern olfactory detection threshold testing, the subject is required to report which of two or more stimuli (i.e., an odorant and one or more blanks) smells strongest, rather than to simply indicate whether an odor is perceived or not. Such "forced-choice" procedures are less confounded by response biases (e.g., the conservatism or liberalism in reporting the presence of an odor under uncertain conditions) than nonforced-choice procedures. In addition, they are more reliable and produce lower threshold values.\textsuperscript{31} The instructions given to a subject are critical in measuring a detection threshold, because if the subject is instructed to report which stimulus produces an odor, rather than which stimulus is stronger, a spuriously higher threshold value may result (odor quality is present only at higher perithreshold concentrations).

The recognition threshold is defined as the lowest concentration where odor quality is reliably discerned. Unfortunately, it is nearly impossible to control criterion biases in recognition threshold measurement. Thus, in a forced-choice situation, guesses are rarely randomly distributed among alternatives, potentially leading to a spuriously low recognition threshold for the preferred alternative. A classic example of this problem comes from taste psychophysics, where some subjects report "sour" much more
frequently than the other primary qualities in the absence of a clearly discernible stimulus, resulting in a spuriously low sour-taste recognition threshold measure.\textsuperscript{113}

A third type of threshold is the \textit{differential threshold}, the smallest amount by which a stimulus must be changed to make it perceptibly stronger or weaker. The size of the increment in odorant concentration ($\Delta I$) required to produce a "just noticeable difference" increases as the comparison concentration ($I$) increases, with the ratio approximating a constant (i.e., $\Delta I/I = C$). This phenomenon was described by Weber in 1834 and was termed "Weber's Law" by Fechner in 1860.\textsuperscript{40} Although differential thresholds have been measured in olfaction, they have received little practical application.

Two types of psychophysical detection threshold procedures have received the most use in the last two decades: the ascending method of limits procedure (AML) and the single staircase procedure (SS).\textsuperscript{23,28} In the AML procedure, odorants are presented sequentially from low to high concentrations, and the point of transition between detection and no detection is estimated. In the SS method, the concentration of the stimulus is increased after trials on which a subject fails to detect the stimulus and decreased after trials where correct detection occurs. An average of the up-down transitions ("reversals") is used to estimate the threshold value. In both the AML and SS procedures, the direction of initial stimulus presentation is made from weak to strong in an effort to reduce potential adaptation effects of prior stimulation. The stability or reliability of a threshold measure is predictably related to the number of trials presented. Hence, procedures with more trials focused in the perithreshold region, such as the SS procedure, produce less variable and more reliable measures than simple AML procedures.\textsuperscript{31}

For the most part, when an individual has a high threshold (i.e., is less sensitive) to one compound, he or she has high thresholds to other compounds as well. This is because most odors depend on the activation of more than one type of receptor and because odorants often share common subsets of receptor types. Because the various types of receptors are interspersed irregularly throughout the epithelium, damage to one region of the epithelium influences the perception to many, indeed probably most, odorants. Theoretically, the degree to which different odors are altered by subtotal damage to the epithelium could vary idiosyncratically, depending on the extent to which each odorant depends on common or disparate receptor types, the relative frequencies of such receptor types, and the number of receptor types activated by each odorant. Nonetheless, as a general rule, detection threshold sensitivity to one compound is correlated to that of other compounds, thus explaining why a detection threshold measure to a single chemical can typically be used clinically to establish the degree of overall olfactory function.
Although there is suggestion that tests of identification or discrimination are more sensitive than tests of odor threshold to lesions in the central olfactory pathways, lesions of the olfactory epithelium can also influence odor identification and discrimination test scores. Furthermore, some studies have found that central brain lesions can, indeed, influence odor detection thresholds. Hence, one cannot reliably infer the locus of the underlying neuropathology from psychophysical test results. Indeed, it is not even clear whether or to what degree many nominally disparate olfactory tests actually measure dissimilar perceptual attributes. Thus, in one study, nine nominally different olfactory tests (e.g., tests of odor identification, discrimination, detection, memory, and suprathreshold intensity and pleasantness perception) were administered to 97 health individuals representing both sexes and a wide range of ages.35 A principal components analysis performed on the correlation matrix among the tests revealed four meaningful components. The first received strong primary loadings from most of the olfactory test measures (including tests of odor identification, discrimination, and threshold), whereas the second was composed of primary loadings from intensity ratings given to a set of suprathreshold odorant concentrations. The third and fourth components had primary loadings that reflected, respectively, mean suprathreshold pleasantness ratings and a response bias measure derived from a yes/no odor identification signal detection task. The results of this study suggest that, at least in healthy subjects spanning a wide age range, several nominally distinct tests of olfactory function are measuring a common source of variance.

LOSS OR ALTERATION OF OLFACTORY FUNCTION FROM CHEMICAL EXPOSURE

The medical and toxicologic literature is replete with reports of smell loss or distortion in humans after acute or chronic exposure to a number of volatile chemicals. Because a detailed assessment of all of these reports is impossible within the scope of this article, we briefly summarize data in this section from two major reviews that have appeared on this topic and focus on compounds for which more sound empirically-based data are available.

Naus77 listed several early and mainly European studies of smell dysfunction after workplace exposure to airborne agents. Most of these studies used some form of odor threshold task and reported adverse effects on the ability to smell dusts and heavy metals (e.g., spices, flour, cotton, lead, coal, mercury, cadmium, coke, grain, SiO₂, tobacco, paper, cement, ashes) and industrial volatile chemicals (e.g., perfumes, menthol, carbonic disulfide, benzene, dichloromethane, pentachlorophenolate, ammonia,
bromine, trichloroethylene, nitrous gases, acids). In the reviewed studies, Naus further sought associations between the presence of hyposmia and factors such as cigarette smoking and duration of exposure. Unfortunately, the studies examined were heterogeneous in terms of methods, and their means for assessing olfactory function were non-forced-choice, thereby confounding the examinee's response criterion with the measure of sensory sensitivity. Importantly, many of these studies, as well as Naus' own analyses, did not use control groups or take into account such basic confounding as the association of age with duration of chemical exposure. Age alone is known to be associated with decreases in olfactory function. Be as it may, Naus' pioneering review mustered convincing evidence for toxin-induced hyposmia in several industrial settings.

More recently, Amoore listed more than 120 different compounds and industrial processes reported to adversely affect olfactory function, a number of which were mentioned by Naus. More than 75 of the studies cited by Amoore examined the relationship between exposure and olfactory dysfunction. Most were case reports or case series, however, and quantitative assessment of function was the exception, rather than the rule. Furthermore, because of the general lack of good industrial hygiene practices during much of the period reviewed, reported exposure levels were mainly rough estimates. Compounds listed by Amoore for which there is at least some empirical basis for adverse influences on smell function are listed in Table 1.

In addition to losses of smell function, perversions of the sense of smell or untoward irritative effects can result from some toxic exposures. For example, Emmet described the case of a pipe fitter exposed to tetrahydrofuran-containing pipe cement who complained of a constant unpleasant smell (parosmia); recovery occurred after removal of exposure to the pipe cement. Shusterman and Sheedy described a woman exposed to chloramine gas who complained of a "stinging" in the nasopharynx in response to common household odors from which she eventually recovered.

EMPIRICAL STUDIES OF VOLATILE TOXIC EXPOSURES ON HUMAN Olfactory FUNCTION

Several classes of chemicals have been clearly implicated in altering the ability to smell, as noted in detail below. Although some studies have not used statistical techniques to unconfound age with duration of exposure, the frequency of the reports and the magnitude of the effects are so large for most of the toxins evaluated that age confounding is likely inconsequential. The largest group of these studies has focused on workers exposed to cadmium and nickel.
Table 1. SUBSTANCES OR INDUSTRIAL PROCESSES THAT REPORTEDLY ADVERSELY ALTER THE SENSE OF SMELL AND FOR WHICH THERE IS REASONABLE SUPPORTIVE SCIENTIFIC DATA

<table>
<thead>
<tr>
<th>Metallic compounds</th>
<th>Organic compounds</th>
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<tbody>
<tr>
<td>Cadmium compounds</td>
<td>Acetone</td>
</tr>
<tr>
<td>Cadmium oxide</td>
<td>Acetophenone</td>
</tr>
<tr>
<td>Chromate salts</td>
<td>Benzene</td>
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<tr>
<td>Nickel hydroxide</td>
<td>Benzine</td>
</tr>
<tr>
<td>Zinc chromate</td>
<td>Butyl acetate</td>
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<tr>
<td>Metalurgical processes</td>
<td>Chloromethanes</td>
</tr>
<tr>
<td>Chromium plating</td>
<td>Ethyl acetate</td>
</tr>
<tr>
<td>Lead smelting</td>
<td>Menthol</td>
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<tr>
<td>Magnet production</td>
<td>Pentachlorophenol</td>
</tr>
<tr>
<td>Mercury (chronic intoxication)</td>
<td>Trichloroethylene</td>
</tr>
<tr>
<td>Nickel plating</td>
<td>Dusts</td>
</tr>
<tr>
<td>Nickel refining (electrolytic)</td>
<td>Cement</td>
</tr>
<tr>
<td>Silver plating</td>
<td>Chemicals</td>
</tr>
<tr>
<td>Steel production</td>
<td>Hardwoods</td>
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<tr>
<td>Zinc production</td>
<td>Lime</td>
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<tr>
<td>Nonmetallic inorganic compounds</td>
<td>Printing</td>
</tr>
<tr>
<td>Ammonia</td>
<td>Silicosis</td>
</tr>
<tr>
<td>Carbon disulfide</td>
<td>Manufacturing processes</td>
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<tr>
<td>Carbon monoxide</td>
<td>Acids</td>
</tr>
<tr>
<td>Chlorine</td>
<td>Asphalt</td>
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<tr>
<td>Hydrazine</td>
<td>Cutting oils</td>
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<tr>
<td>Nitrogen dioxide</td>
<td>Fragrances</td>
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<tr>
<td>Sulfur dioxide</td>
<td>Lead paints</td>
</tr>
<tr>
<td>Fluorides</td>
<td>Paprika</td>
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<td></td>
<td>Spices</td>
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<td></td>
<td>Tobacco</td>
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<tr>
<td></td>
<td>Varnishes</td>
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<tr>
<td></td>
<td>Wastewater (refinery)</td>
</tr>
</tbody>
</table>


Cadmium and Nickel

Cadmium is a highly toxic trace metal involved, often along with nickel, in several manufacturing processes. The National Institute for Occupational Safety and Health estimates that 100,000 Americans are exposed occupationally to cadmium fumes or dust in industries such as electroplating and battery manufacturing. Industrial exposure to cadmium has long been suspected as having adverse effects on the human ability to smell, and empirical studies of cadmium’s effects on smell date back to the late 1940s and early 1950s. In 1952, Baader reviewed the effects of chronic cadmium poisoning on the nasal mucosa, noting edema, rhinitis, and general atrophy in selected cases.

In a pioneering report on this topic, Friberg noted that 44% of 43 workers employed in an alkaline battery factory exposed to both
cadmium-iron dust (5–15 mg/m³ of air) and nickel graphite dust (10–150 mg/m³ of air) for periods ranging from 9 to 34 years complained of decreased ability to smell. On sensory examination, approximately one third of these workers were reportedly anosmic, although the nature of the olfactory testing was not reported. Only 10% of 15 workers employed in the same areas of the factory for four years or less complained of this problem; none were apparently tested for their smell ability.

Ten years after the Friberg study, Adams and Crabtree1 found, in a study of 106 cadmium- and nickel-dust-exposed alkaline battery workers and 84 matched normal controls that the exposed individuals performed significantly more poorly than the controls on an odor threshold test using phenol. In this study, 27% of the exposed workers were reportedly anosmic, compared with 5% of the controls. Although the amount of exposure to cadmium could only be roughly estimated, in some factory sites it apparently reached levels as high as 2.76 mg/m³. Approximately half of the anosmic workers were unaware of their disorder. Despite the fact that examination of the nasal mucosa failed to yield any relationship between degree of irritation and olfactory dysfunction, proteinuria was positively correlated with the presence of anosmia.

A report of even a higher prevalence of anosmia among workers exposed to cadmium appeared four years later. Potts84 reported that 64% of 70 workers exposed to cadmium dust (.6–236 mg/m³ of air) in a section of a battery factory for 10 to 40 years were anosmic. Unfortunately, no description was made in this study as to whether or how the smell testing was carried out.

Three studies have appeared on this topic in the more modern era. In the first of these studies, Yin-Zeng et al18 found that 28% of individuals who had worked five years or more in a cadmium-refining plant reported having anosmia. No olfactory measures were apparently taken. The average concentration of airborne cadmium was said to be comparatively low (between 0.004 and 0.187 mg/m³), but still slightly above the current Occupational Safety and Health Administration Permissible Exposure Limit of 0.005 mg/m³ to which a worker may be exposed. In the second of these studies, Rose et al91 administered a butanol odor detection threshold test and an odor discrimination test to 55 workers exposed for an average of 12 years to cadmium fumes (from brazing refrigerator coils). Airborne cadmium, measured for the first time 13 years after production began, was 0.300 mg/m³. Workers with the highest body burden of cadmium, as measured by urinalysis, exhibited moderate to severe hyposmia, but not anosmia, on the detection threshold task, but performed normally on the odor discrimination task. These observations led the authors to the questionable conclusion that only peripheral, and not central, elements of the olfactory pathway were damaged. In the third study, Sulkowski et al93
compared the olfactory function of 73 workers involved in the production of cadmium-nickel batteries to that of 43 nonexposed, age- and smoking-matched controls. Anosmia or hyposmia was found in 45.2% of the exposed group and in 4.6% of the controls. Unfortunately, the Elsberg blast injection procedure was used to assess olfactory function. This procedure has been criticized on numerous grounds, including (1) the lack of a forced-choice response (which results in artificially elevated threshold values), (2) the confounding of pressure with the number of molecules in the stimulus, (3) the introduction of a very unnatural stimulus pulse into the nose, and (4) the production of unreliable threshold measures. Despite its shortcomings, however, this study is in accord with earlier ones in implying that, even at low concentrations, cadmium exposure can result in loss of smell function.

**Chromium**

Like cadmium, chromium is often used with nickel and other metals in industrial situations, most notably in the manufacture of high-quality steel alloys. Unlike cadmium, there has been relatively little research about the effects of chromium on the ability to smell, even though this metal has long been suspected as having an adverse influence. Watanabe and Fukuchi examined odor detection and recognition thresholds of 26 male and 7 female employees of a chromate-producing factory who had worked there for at least seven years. Over half of the subjects (51.4%) were noted as having perforated nasal septa; 54.5% exhibited elevated smell thresholds to the five odorants evaluated (phenyl ethanol, cyclopentenolone, isovaleric acid, γ-undecalactone, scatol), with two reportedly being anosmic. Although the degree of olfactory function was not related to the presence of the septal perforations, it was related to the duration of employment in the factory.

**Mercury**

Although mercury exposure occurs in a number of industrial operations and reportedly produces olfactory deficits, like chromium, the data in support of this contention are limited. In fact, the sole empirical study used patients (mean age, 79 years) suffering from Minamata disease developed through exposure to in utero mercury. The patients and controls were administered the UPSIT and an odor detection threshold test using phenyl ethyl alcohol. The patients with Minamata disease exhibited greater age-related declines in both threshold sensitivity and UPSIT scores than did age-matched controls. In an autopsy study of patients with chronic Minamata disease, damage to the olfactory bulb and tract was found, although no obvious changes in the nasal epithelium were observed. Whether this
is because the mercury exposure was due to ingestion and not inhalation is unknown.

Lead

Inorganic and organic lead can alter CNS neurotransmitters and can produce transient or possibly permanent difficulties in attention or concentration, manual dexterity, memory, visuoconstruction, psychological well-being, and psychomotor speed and accuracy. Whether and to what degree this metal alters the ability to smell is not clear, although the available evidence suggests that occupational exposure to lead has only minor effects, if any. Surprisingly, no studies are available on children who have been exposed to lead, despite the fact that the pediatric population is more sensitive to neurotoxic effects of exposure to low levels of lead.

Schwartz et al administered the UPSIT, along with several neuropsychological tests, to 222 employees of a tetraethyl lead manufacturing plant. The testing was performed on site, prior to or in place of a work shift, to minimize any possible acute toxic effects and to reduce work-related fatigue. Industrial hygiene sampling data were available, and duration of exposure to lead was estimated from personnel records and from detailed occupational histories compiled by trained occupational medicine physicians. In this subject population, organolead production peaked in the late 1960s and early 1970s, and urine lead levels showed an upward trend from 1965 through 1985, followed by a decline. Mean differences in the test scores were estimated by comparing the average scores of the moderate, high, and highest exposure groups to those of the low exposure (reference) group and by adjusting for the confounding influences of age, intellectual ability, race, and alcohol consumption. No influence of lead on UPSIT scores was apparent, even though lead exposure was associated with decrements in a several the neuropsychological measures.

Subsequently, Bolla et al compared UPSIT data from a subset (n = 190) of the aforementioned lead-exposed subjects to those from 144 solvent-exposed workers and 52 reference subjects who had been administered the same set of sensory and neuropsychological tests. Again, the overall results showed that, after adjusting for confounding variables such as age, vocabulary score, and race, the UPSIT scores of lead-exposed workers did not differ significantly from those of the reference group (respective mean scores, 36.4 and 36.9). However, when the lead-exposed workers were divided into exposure durations of less than 11 years, 11 to 17 years, and more than 17 years, significantly lower UPSIT scores were noted relative to the reference group, for the 11 to 17-year exposure group, but not for the other two groups. This effect was apparently not viewed by the authors as meaningful, as they state in the conclusion of the article, “Olfactory function was . . . unaffected by lead exposure”.

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Solvents

Workers in many occupations, including painting and paint manufacturing, lumber and furniture fabrication, machining operations, equipment cleaning and degreasing, and floor and carpet laying, are exposed over time to significant levels of solvents, such as acetone, methyl ethyl ketone, and tetrahydrochloride, often in closed quarters. Evidence that exposure to such solvents may influence smell ability ranges from self-reported disturbances of smell function in floor-layer workers exposed to high levels of toluene to sophisticated case-control studies of long-term exposure to solvents in manufacturing plants. Because of their lipophilicity, solvents can readily cross the nasal mucosa and penetrate underlying cellular membranes. Such agents can also enter the bloodstream through the nasal capillaries and can cross the blood–brain barrier, producing in extreme cases (e.g., in chronic glue sniffers), atrophy of central brain structures (e.g., frontal lobes, cerebellum).

Ahlstrom et al. found that fuel oil tank cleaners exhibit higher detection thresholds for n-butanol and fuel oil vapors than controls, whereas this was not the case for pyridine and dimethyl disulfide. The elevated thresholds, however, did not fall outside of the normal range. The authors noted, for all stimuli evaluated, that the workers exhibited relatively normal perception of strong stimuli, but impaired perception of weak stimuli. The largest decrement was found for detection of fuel oil vapor. This observation is in accord with the concept of “industrial anosmia,” where exposure to strong odors in the workplace results in a reduction in sensitivity that is confined to those particular odors. Such effects may reflect long-term adaptation because, unlike the effects resulting from exposure to toxic metals, they are typically reversible, disappearing after a worker is removed for a period from the exposure area.

Schwartz et al. evaluated the effects of chronic, low-level solvent exposure on olfactory function in 187 workers at a paint formulation plant. As in their lead exposure research, industrial hygiene sampling data and detailed occupational history data from personnel records were used. A significant dose-related adverse effect of solvent exposure on UPSIT scores was documented, but only in never-smokers.

Recently, Mergler and Beauvais examined detection thresholds for toluene and phenyl ethyl methyl ethyl carbinol in five volunteers who were experimentally exposed for seven-hour periods to either toluene, xylene, or a mixture of these two agents in an order counterbalanced using Latin squares. A sixfold shift in the detection threshold for toluene was found immediately after exposure to toluene, xylene, or their mixture. No differences were found in phenyl ethyl methyl ethyl carbinol thresholds after exposure to any of the compounds. Because the alterations in olfactory function were reversible, the shift in detection threshold is again likely
caused by odor adaptation, rather than by direct toxic insult to the olfactory receptor neurons.

In contrast to the aforementioned studies, Sandmark et al\(^9^4\) found no long-term influences of solvent exposure on smell function in a group of 54 painters exposed to organic solvents relative to 42 unexposed controls. When the confounding influences of age and smoking habits were controlled for, no differences in UPSIT or pyridine threshold test scores were noted between the two groups. The lack of an effect was attributed to the low-to-moderate degree of exposure to the solvents.

**Irritant Gases**

Numerous empirical studies report olfactory deficits after accidental exposure to high concentrations of irritant gases. Such irritants as ozone and formaldehyde are common components of both indoor and outdoor pollution, combustion products in tobacco smoke, and exhaust from automobile and other internal combustion engines. Although chronic exposure to low levels of irritative airborne contaminants occur in a number of neighborhoods and workplaces, it does not necessarily follow that nasal irritation, per se, translates into loss of olfactory function. Indeed, some nasal irritants have no clear smell. Nonetheless, one would expect an association between an odorant’s irritative properties and its propensity to alter smell function if continued irritation of the mucosa leads to necrosis and other problems. Furthermore, a large animal literature (mainly rodent) supports the idea that chronic exposure to several irritants can, at higher concentrations, damage the olfactory epithelia.

Formaldehyde, an ubiquitous and highly reactive gas, is used in a variety of manufacturing processes and in biology classes, hospital and university histology departments, mortuaries, and other situations where preservation or fixing of tissue is required. This gas is absorbed mainly in the nose. Although exposure to formaldehyde is often alleged to decrease olfactory acuity,\(^1^0^3\) only two human studies have reported an adverse effect of this agent on the ability to smell. In the first, workers exposed to 0.075 to 0.750 ppm formaldehyde (alone or in combination with wood dust) showed a slight but significant elevation in detection thresholds (serial dilutions of pyridine) when compared to controls (14.2 vs 15.6).\(^5\) In the second, a questionnaire administered to histology technicians regularly exposed to 0.200 to 1.900 ppm formaldehyde revealed that 68% reported decreased odor perception. Only 9% of the control group did so.\(^6^0\)

In the most extensive systematic investigation of toxic chemicals on the human ability to smell to date, Schwartz et al\(^9^8\) administered the UPSIT to 731 chemical workers exposed to acrylic acid and a variety of acrylates and methacrylates at levels typically below their threshold limit.
values. Although analysis of the cross-sectional data revealed no relationship between chemical exposure and olfactory deficits, a nested case-control study designed to examine cumulative effects of exposure uncovered several associations: (1) olfactory function decreased with increased cumulative exposure; (2) the effects appeared to be reversible; and (3) the highest relative risk of olfactory dysfunction occurred in workers who had never smoked. The similarity of the latter phenomenon to that found in the previously mentioned solvent study illustrates how ancillary factors can determine the expression of the olfactory toxicity of some compounds.

Recently, Dalton et al.20 investigated whether occupational exposure to styrene altered smell function. Exposure histories were reconstructed using industrial hygiene data, and the workers were tested using a battery of olfactory tests, including tests of odor identification ability, detection threshold sensitivity to phenyl ethyl alcohol and styrene, and retronasal odor perception. No significant differences were found between exposed workers and matched controls on any of the tests, except for the styrene thresholds, which were significantly elevated in the workers. The latter phenomenon was interpreted as being caused by exposure-induced adaptation.

Workplace exposure to several irritants that are major components of air pollution has also been associated with loss of olfactory function. Harada et al.49 reported that exposure to sulfur dioxide and ammonia produced an elevation in odor detection thresholds for five substances that were evaluated. Several of these workers complained of olfactory dysfunction. Similarly, repeated exposure of human volunteers to 0.4 ppb of ozone for four hours per day for four days produced initial elevations in detection thresholds to butanol that returned to normal soon after cessation of the exposure.85

Chemical Exposure and the Multiple Chemical Sensitivity Syndrome

There are proponents of the notion that a wide variety of somatic symptoms, including hypersensitivity to odors, depression, anxiety, fatigue, general malaise, mental confusion, lightheadedness, headache, insomnia, myalgia, loss of appetite, and numbness, can be elicited by single or multiple exposures to extremely low concentrations of several common household or industrial chemicals. Such symptoms occur without documentable signs of medical disease.92 This unorthodox complex of apparent chemically induced symptoms was first termed "environmental illness" or "chemical reactivity" by Randolph in the 1960s.86 Cullen subsequently termed this complex of chemically induced symptoms multiple chemical sensitivities (MCS) and developed an operational case definition of the disorder.18 Cullen confined the definition to a subgroup of
"environmentally sensitive" patients and set seven criteria for its definition: (1) some documentable environmental exposure(s), illness(es) or insult(s) were coincident with the onset of the problem; (2) the symptoms are associated with more than one organ system; (3) the symptoms recur and abate in response to predictable stimuli; (4) the symptoms are elicited by chemicals of diverse classes and toxicologic modes of action; (5) the symptoms are elicited by exposures that are demonstrable (albeit of low level); (6) the symptoms cannot be explained by a single, widely available test of organ system function; and (7) exposures that elicit symptoms are very low—"(i.e., many standard deviations below "average" exposures known to cause adverse human response . . . generally lower than 1% of the established threshold limit values for toxicity)." Some of the agents that have been reported to induce these symptoms include perfumes, drugs, organic solvents, combustion exhausts, soaps, insecticides, preservatives, cigarette smoke, fragrances, perfumes, and colognes.

Although not all patients with the putative MCS syndrome report heightened smell sensitivity, enough have done so to catalyze two empirical studies on this topic. In both cases, no evidence of altered odor detection threshold sensitivity was found. In the first, the detection threshold values of 18 patients with putative MCS did not differ significantly from those of matched controls for the solvent methyl ethyl ketone and the rose-like smelling agent phenyl ethyl alcohol.27 In the second, detection thresholds of 23 MCS subjects and 23 controls to phenyl ethyl alcohol also did not differ from one another.54 Paradoxically, in the latter study, the MCS subjects were inferior to normal controls in identifying and discriminating among suprathreshold odors and exhibited smaller odor-induced event-related potentials. Assuming the validity of these findings, this study implies that the suprathreshold olfactory function of MCS patients is decreased, not increased.

MECHANISMS OF TOXIN-INDUCED OLFACTORY LOSS

It should be noted that many chemicals potentially damaging to the olfactory system activate intranasal protective reflexes, mainly through the trigeminal nerve, that minimize their penetration into the nasal passages.**

**It is noteworthy that the reflexive depression in respiratory rate induced by exposure to a sensory irritant (which is mainly caused by stimulation of intranasal or pharyngeal trigeminal afferents) has been used extensively in the establishment of the OSHA Permissible Exposure Limit (PELs) and the American Conference of Governmental Industrial Hygienist's (ACGIH) Threshold Limit Values (TLVs). Indeed, exposure limits for approximately one third of the compounds regulated by OSHA have been based, at least in part, on their irritant properties. For a new irritative compound, the concentration at which it depresses respiratory rate by 50% is typically first established (RD50). A value of 0.03 X RD50 is then calculated; for many compounds, this value has been found to be very close to the established TLV.
Such reflexive mechanisms include rejection responses (e.g., sneezing, halting of inhalation), increased engorgement of the erectile tissue in the nasal passages, and increased mucus secretion. Unfortunately, although such mechanisms reduce exposure to irritating chemicals to some degree, they do not always protect the olfactory system from inhaled chemicals, particularly ones that do not active trigeminal nerve afferents or are present on a chronic basis.

Animal studies suggest that the primary means by which chemicals alter olfactory function is by direct interaction with the olfactory epithelium, where they damage the olfactory receptors and associated cells. Agents such as dimethylamine and 3-methylfuran damage the epithelium indirectly by producing metabolic byproducts that, in turn, damage the mucosa. The speed by which restoration occurs after the sloughing off of the epithelium depends on the concentration and species of the chemicals involved. For some substances, restoration occurs in a few weeks, whereas for others it can take months. In general, the degree of reconstitution depends on the degree of insult; poor reconstitution is expected when the lamina propria and Bowman’s glands become heavily damaged.

As shown in Table 2, a variety of exogenous agents damage the olfactory membrane of rodents. Unfortunately, the degree to which such data generalize to humans is not known. Although olfactory epithelial tissue can be obtained in living humans via endoscopic spot biopsy, there are sampling issues involved, and no such study has been performed in toxin-exposed human populations. Furthermore, no cadaver study has yet been performed in such groups. Rodents, in addition to being obligate nose breathers, possess maxillary turbinates and an additional row of ethmoidal turbinates, resulting in a more complex distribution of airflow patterns and nasal absorption distribution of chemicals than seen in humans.

The limited data available suggest that the rodent olfactory epithelium may be more resilient than the human olfactory epithelium to toxic damage from some agents, perhaps reflecting differences in xenobiotic metabolism. In one study, for example, adult male rats were exposed to relatively high levels of airborne cadmium (0.500 mg/m³) for 20 weeks. Unlike the situation with humans, no evidence of pathologic alterations of either the olfactory or nasal respiratory epithelia was present, and behavioral tests were unable to document any cadmium-related adverse effect on detection threshold sensitivity. This is in spite of the fact that lung and cardiac toxicity were found. Although similar rodent studies (using nickel and chromium) have found nickel-related damage to the olfactory epithelium, behavioral deficits were not observed.

The nasal and olfactory mucosa possess several chemical defense mechanisms in addition to those mentioned to thwart invasion of
xenobiotic and pathogenic agents. For example, they are capable of secreting antibodies and antimicrobial proteins, such as lactoferrin and lysozyme to deal with inhaled pathogens. The nasal passages are also protected by the presence of phase I and phase II enzymes (i.e., cytochrome P-450s, glutathione, and related enzymes) found in concentrations that can be greater on a per gram basis than in the liver or lungs. The source of such agents in the olfactory epithelium is the supporting cells and the Bowman’s glands, ensuring their presence in the mucus of the region. In some cases, chronic exposure to low doses of toxic compounds induces an enzymatic metabolic protective status so that subsequent higher exposures produce little or no toxicity.

Some olfactory toxicants produce acute or chronic inflammation that, in addition to limiting airflow to the olfactory region or inducing metabolic toxins in the epithelium, can ultimately damage the epithelium. Such inflammation can also decrease upper airway immunoglobulin A, thereby allowing for colonization of the olfactory mucosa with pathologic bacteria that can have adverse effects on the mucosa. In rare cases, volatile chemicals can increase mucosal cellular proliferation that can lead to neoplastic processes that themselves can alter the ability to smell. Increased prevalence of nasal and sinus carcinomas have been noted in workers exposed to nickel dust, ionizing radiation, wood dust, formaldehyde, and leather dust.

Toxic effects of airborne chemicals on the olfactory neuroepithelium can result from the synergism of several factors. For example, because of weakened defense mechanisms, concurrent exposure to a toxic compound during an upper respiratory infection may result in much greater damage than exposure to either alone. Conversely, cigarette smoking may protect against solvent-induced olfactory deficits of chemical workers. Estrogens and some other hormones may mitigate olfactory epithelial damage produced by neurotoxins such as 3-methyl indole.

Attempts to ameliorate the dysfunction resulting from exposure to toxic compounds are limited. In some instances, inhibition of enzymatic pathways that produce toxins can eliminate the damaging effects of such chemicals as dimethylamine and 3-methylfuran. Topical steroids, which are routinely used for alleviation of rhinitis and polyposis, may do more than simply increase airway patency by shrinking inflamed tissue. Thus, they may hasten the reconstitution of the olfactory epithelium after insult, although large doses may have an adverse effect. As we increase our understanding of the factors that regulate neurogenesis and apoptosis in the olfactory epithelium, and of the factors involved in the guidance of axonal propagation through the cribriform plate, new therapeutic avenues will undoubtedly present themselves.
<table>
<thead>
<tr>
<th>Compound</th>
<th>Duration</th>
<th>Effects on Histology and Function</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaldehyde (400-5000 ppm)</td>
<td>6 hr/d 5 d/wk 1-28 mo</td>
<td>Degeneration, metaplasia, loss of Bowman’s glands and nerve bundles, adenomas, squamous cell carcinomas</td>
<td>7, 116, 117</td>
</tr>
<tr>
<td>Acrolein (1.7 ppm)</td>
<td>6 hr/d 5 d</td>
<td>Hypertrophy, hyperplasia, erosion, ulceration, necrosis inflammation</td>
<td>17</td>
</tr>
<tr>
<td>Acrylic acid (5-75 ppm)</td>
<td>6 hr/d 5 d/wk 13 wk</td>
<td>Degeneration, replacement with respiratory epithelium, inflammation, hyperplasia of Bowman’s glands</td>
<td>73</td>
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<tr>
<td>Benomyl (50-200 mg/m³)</td>
<td>6 hr/d 6 d/wk 13 wk</td>
<td>Degeneration</td>
<td>111</td>
</tr>
<tr>
<td>Bromobenzene (25 mol/kg ip)</td>
<td>[5 min–3 d]*</td>
<td>Degeneration of olfactory epithelium and Bowman’s glands</td>
<td>13</td>
</tr>
<tr>
<td>Cadmium (250-500 g/m³)</td>
<td>5 hr/d 5 d/wk 20 wk</td>
<td>Little change</td>
<td>105</td>
</tr>
<tr>
<td>Chlorine gas (0.4-11 ppm)</td>
<td>6 hr/d 5 d/wk 16 wk</td>
<td>Degeneration, septal perforations, intracellular deposits of eosinophilic material, mucus cell hypertrophy</td>
<td>16, 56, 115</td>
</tr>
<tr>
<td>Chloroform (300 ppm)</td>
<td>6 hr/d 7 d</td>
<td>Degeneration of Bowman’s glands, cell proliferation in periosteum and bone</td>
<td>71</td>
</tr>
<tr>
<td>Chloropicrin (8 ppm)</td>
<td>6 hr/d 5 d</td>
<td>Hypertrophy, hyperplasia, ulceration, necrosis, inflammation</td>
<td>16</td>
</tr>
<tr>
<td>Coumarin (50 mg/kg ip)</td>
<td>[48 hr]</td>
<td>Necrosis, cell loss, and basal cell metaplasia in the olfactory mucosa</td>
<td>119</td>
</tr>
<tr>
<td>Chlorthiamid (6-50 mg/kg ip)</td>
<td>[8 hr–7 d]*</td>
<td>Degeneration of olfactory epithelium and Bowman’s glands, replacement with respiratory epithelium, fibrosis in lamina propria</td>
<td>14</td>
</tr>
<tr>
<td>Dibasic esters (20-900 mg/m³)</td>
<td>4 hr/d 7-13 wk</td>
<td>Degeneration, sustentacular cells injured initially, cell proliferation</td>
<td>10, 59</td>
</tr>
<tr>
<td>1,2 dibromo-3-chloropropene</td>
<td>6 hr/d 5 d/wk 13 wk</td>
<td>Degeneration, metaplasia, hyperplasia</td>
<td>90</td>
</tr>
<tr>
<td>(5-60 ppm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,2 dibromo ethane (3-75 ppm)</td>
<td>6 hr/d 5 d/wk 13 wk</td>
<td>Degeneration, metaplasia, hyperplasia</td>
<td>90</td>
</tr>
<tr>
<td>Dichlophenil (12-50 mg/kg ip)</td>
<td>[8 hr–7 d]*</td>
<td>Degeneration of olfactory epithelium and Bowman’s glands</td>
<td>12</td>
</tr>
<tr>
<td>(30–150 ppm)</td>
<td></td>
<td>Degeneration and metaplasia</td>
<td>66, 104</td>
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<tr>
<td>Dimethylamine (10-511 ppm)</td>
<td>6 hr/d 5 d/wk 6-12 mo</td>
<td>Degeneration, loss of nerve bundles, hypertrophy of Bowman’s glands</td>
<td>16, 17</td>
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<tr>
<td>1,4 dithiane (105-420 mg/kg ip)</td>
<td>[90 d]*</td>
<td>Anisotrophic crystals in giant cells (undetermined chemical composition)</td>
<td>95</td>
</tr>
<tr>
<td>Epichlorohydrin (687 ppm)</td>
<td>6 hr/d 5 d</td>
<td>Ulceration, necrosis</td>
<td>16</td>
</tr>
<tr>
<td>Ferrocene (3-30 mg/m³)</td>
<td>6 hr/d 5 d/wk 13 wk</td>
<td>Iron accumulation, necrotizing inflammation, metaplasia</td>
<td>79</td>
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<tr>
<td>Formaldehyde (0.25-15 ppm)</td>
<td>6 hr/d 5 d/4 mo</td>
<td>Decrease number of bipolar cells, increase number of basal cells, degeneration of nerve bundles, reduced odor discrimination</td>
<td>5, 6</td>
</tr>
<tr>
<td>Compound</td>
<td>Duration(s)</td>
<td>Description</td>
<td></td>
</tr>
<tr>
<td>----------------------------------------------</td>
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<td>------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Furfural (250–100 ppm)</td>
<td>7 hr/d 5 d/wk 52 wk</td>
<td>Disorientation of sensory cells, degeneration of Bowman’s glands, cystlike structures in lamina propria</td>
<td></td>
</tr>
<tr>
<td>Furfural alcohol (2–250 ppm)</td>
<td>13 wk</td>
<td>Squamous and respiratory metaplasia of olfactory epithelium, inflammation, hyaline droplets, squamous metaplasia of ducts</td>
<td></td>
</tr>
<tr>
<td>Hexamethylene di-isocyanate (0.005–175 ppm)</td>
<td>6 hr/d 5 d/wk 12 mo</td>
<td>Degeneration, mucus hyperplasia</td>
<td></td>
</tr>
<tr>
<td>Hydrazine (75–750 ppm)</td>
<td>1 hr/d 1–10 d</td>
<td>Degeneration</td>
<td></td>
</tr>
<tr>
<td>β,β′-iminodi-propionitrile (200–400 mg/kg ip)</td>
<td>[6 hr–56 d]*</td>
<td>Degeneration of axon bundles, increase of glial fibrillary acidic protein</td>
<td></td>
</tr>
<tr>
<td>Methyl bromide (200 ppm)</td>
<td>4 hr/d 4 d/wk</td>
<td>Degeneration, decreased carnosine, behavioral deficits</td>
<td></td>
</tr>
<tr>
<td>3-methylfuran (148–322 mol/l)</td>
<td>1 hr</td>
<td>Degeneration, more severe in rats than hamsters</td>
<td></td>
</tr>
<tr>
<td>3-methylindole (100–400 mg/kg ip)</td>
<td>[7–90 d]*</td>
<td>Degeneration, fibrous, adhesions, osseous remodeling, Bowman’s gland</td>
<td></td>
</tr>
<tr>
<td>Methyl isocyanate (10, 30 ppm)</td>
<td>2 hr</td>
<td>Hypertrophy, behavioral deficits</td>
<td></td>
</tr>
<tr>
<td>Naphthalene (400–1600 mg/kg ip)</td>
<td>6 hr/d 5 d/wk 13 wk</td>
<td>Degeneration</td>
<td></td>
</tr>
<tr>
<td>Nickel subsulfide (0.11–1.8 mg/m³)</td>
<td>[24 hr]*</td>
<td>Atrophy</td>
<td></td>
</tr>
<tr>
<td>Nickel sulfate (3.5–635 mg/m³)</td>
<td>6 hr/d 12–16 consecutive d</td>
<td>Atrophy, degeneration, decrease in carnosine</td>
<td></td>
</tr>
<tr>
<td>N-nitroso-dimethylamine (20–80 mg/kg ip)</td>
<td>[6 hr–30 d]*</td>
<td>Degeneration of olfactory epithelium and Bowman’s glands</td>
<td></td>
</tr>
<tr>
<td>N-nitroso-pyrrolidine (30–100 mg/kg ip)</td>
<td>[6 hr–30 d]*</td>
<td>Degeneration of olfactory epithelium and Bowman’s glands</td>
<td></td>
</tr>
<tr>
<td>Propylene oxide (10–525 ppm)</td>
<td>4 wk</td>
<td>Degeneration</td>
<td></td>
</tr>
<tr>
<td>Pyridine (5–444 ppm)</td>
<td>6 hr–4 d</td>
<td>Degeneration of olfactory epithelium</td>
<td></td>
</tr>
<tr>
<td>RP 73401 (1 mg/kg/d)</td>
<td>1 hr–5 d</td>
<td>Degeneration of olfactory epithelium and Bowman’s glands</td>
<td></td>
</tr>
<tr>
<td>Sulfur dioxide (10–117 ppm)</td>
<td>72 hr, or 6 hr/d 5 d</td>
<td>Necrosis, edema, destruction, hyerlasia, hypertrophy</td>
<td></td>
</tr>
<tr>
<td>2,4-toluene di-isocyanate (0.4 ppm)</td>
<td>6 hr/d 5 d</td>
<td>Ulceration, necrosis, inflammation, degeneration</td>
<td></td>
</tr>
<tr>
<td>3-trifluoromethyl 1-pyridine (0.1–329 ppm)</td>
<td>[6 hr–90 d]*</td>
<td>Degeneration, reduced Bowman’s activity</td>
<td></td>
</tr>
</tbody>
</table>

* Durations are times postexposure until sacrifice.
CONCLUSIONS

Although the bulk of evidence suggests that toxic chemicals influence human olfactory function by damaging the olfactory neuroepithelium, there is a dearth of information as to whether solvents and other agents adversely influence central olfactory structures. Clearly, studies of the toxic effects of airborne agents on the human olfactory system are still in their infancy, and no human biopsy or cadaver studies of even the olfactory epithelium of chemically exposed humans have been made. Although, at face value, the available data suggest that most industrial chemicals do not damage the olfactory membrane at concentrations below current threshold limit values, few epidemiologic studies on this point have been performed, and longitudinal data are completely lacking. As noted at the beginning of this article, the olfactory epithelium undergoes metaplastic changes throughout life, and the degree to which exposure to even low levels of airborne toxins contributes to such changes is not known. Future studies are needed to establish how generalizable rodent data are to the human condition and whether the human olfactory system is, in fact, cumulatively damaged by intermittent exposure to environmental toxic chemicals.

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