All substances are poisons; there is none which is not a poison. The right dose differentiates a poison and a remedy. — Paracelsus

Paracelsus is the 16th century itinerant physician who became the father of modern toxicology. He realized that there is no absolute definition of poison. Virtually any substance may be toxic depending on the dose. This concept embodies the dose–response relationship, the cornerstone of toxicology. In contrast to an allergic response, which requires immunologic sensitization for a response to occur, a toxic response requires no previous exposure or immunologic sensitization.

Routes of exposure

Routes of exposure to chemical substances include ingestion, injection, dermal absorption, and inhalation. Exposure to chemicals in the workplace or environment most often occurs by inhalation, leading to the possible development of localized respiratory effects, pulmonary absorption, and systemic toxic effects. Although skin absorption of some chemicals may occur, localized skin irritation and development of allergic contact dermatitis are more common manifestations of dermal exposure than are systemic absorption and toxicity.

Types of exposure

Particulates may be produced by crushing, grinding, or naturally occurring mechanisms, such as wind, that release small solid particles. These particles may
be inhaled and produce adverse effects when their physical and chemical properties allow penetration of the lung and consequent pulmonary damage. The physical, rather than chemical, properties of asbestos and silica are important in producing lung injury. Particles greater than 5 μm are trapped in the nares. Particles ranging from 0.5 to 2.5 μm are deposited in the alveoli. Large, insoluble particles are cleared from the airway by the mucociliary escalator and may be swallowed or expectorated. In some work environments (eg, manganese mining, lead smelting), respiratory exposure can lead to secondary ingestion by this mechanism and result in heavy-metal intoxication. Particles that remain in the respiratory tract may be phagocytized within the lung interstitium and create inflammation or fibrosis.

The term “fume” often is applied incorrectly when the term “gas” or “vapor” would be more accurate. Fumes are formed when vapor from molten metal condenses and coalesces into very fine particulates. Welding and smelting are the most common processes that generate fumes. The small size of fume particles (0.001–1.0 μm) allows high penetration into the alveoli.

Processes that produce splashing, foaming, or spraying may produce small droplets that most likely are deposited in the upper airways because of their large size. Mists are more likely to produce injury to the skin and eyes because of the volume of material.

Gases and vapors comprise distinct molecules that mix and diffuse in ambient air from the point of origin or release. Whereas gases are substances that normally exist in the gaseous state, vapors are the evaporative form of liquid substances. The physical behavior of gases and vapors is similar.

Patient evaluation

Medical and occupational history

The evaluation of a patient who potentially has been exposed to a chemical substance begins with a comprehensive medical, occupational, and environmental history. A health questionnaire sent to the patient before evaluation can be a valuable aid in obtaining a detailed and accurate history. Such questionnaires have been published previously [1]. A questionnaire helps prompt the patient to recall the chronology of past health problems and consider specific work practices or consult an employer to obtain the identity of any substances used at the workplace. A questionnaire completed before the clinical interview provides an outline of the patient’s health history from which the physician can explore the details of the patient’s health status before and after an encounter with chemical substances. The patient should be queried about the entire work history rather than just the current job during which the alleged chemical exposure occurred. For each job, work practices, substances used, and protective practices should be reviewed and recorded. The work history also should include any concurrent part-time or self-employed work and hobby.
activities. Any symptoms encountered during each job should be delineated as specifically as possible. The reported timing of the initial onset of each reported symptom, severity, duration, and persistence can be helpful in assessing a possible exposure. For each set of symptoms, the patient should be asked to describe the association to assigned work practices, such as whether: the symptoms arose immediately when using a particular substance; a pattern of recurrent symptoms was established with repeated use; there were associated symptoms; and the symptoms resolved or persisted long after cessation of exposure. Detailed questioning can help characterize symptom onset and progression and reveal a constellation of symptoms that may imply consistency with workplace exposure or suggest an alternative explanation. The nature and severity of the reported symptoms help guide the clinician in the formulation of an efficient diagnostic work-up.

The type of respiratory protective device that is used, if any, should be detailed. The most common form of respiratory protection is the paper dust mask. Although effective for filtering nuisance dusts, most dust masks are not approved for removing many forms of toxic dust, mist, or fumes and are generally ineffective and not recommended for protection against gases or vapors. A chemical-cartridge respirator may provide protection against concentrations of some vapors or gases of up to 1000 ppm if it is fitted with the proper cartridge and if training is provided. If ambient air is entrained from an improperly fitted respirator or saturated cartridge that is not replaced periodically, the worker is at risk for excessive exposure to airborne chemicals. A well-trained or experienced worker changes cartridges according to a schedule or when a break through occurs (ie, the odor of chemical is perceived when the cartridge has become saturated or obstructed with airborne contaminants). Workers who may be exposed to high concentrations of a toxic substance or who work in an enclosed environment may be required to use an air-supply respirator. Supplied air respirators allow workers to breathe clean air that is supplied by a hose or from a pressurized portable tank (eg, self-contained breathing apparatus). A properly functioning air supply respirator is the gold standard for respirators and provides a high level of protection against airborne chemicals.

The occupational history should be supplemented by a review of all past medical records, which enable to physician to corroborate the historical information that is presented in the patient interview. Important risk factors or behaviors that could have a role in symptom expression that were embellished or minimized during the patient interview may have been disclosed to former healthcare providers. A patient’s estimate of a smoking habit may be reduced during an evaluation for a chemically induced respiratory disorder, and previous treatment for past respiratory complaints may be minimized. A complete review of the past records provides a more complete and accurate clinical picture and overcomes some of the difficulties encountered from incomplete recall, mistaken perception, or compensation-related motivation. Past medical records also provide reports of laboratory studies, radiographic data, and other objective
data that may be useful for documentation of diagnoses or comparison with current studies.

**Physical examination**

The physical examination encompasses all organ systems and pays special attention to potential target areas of potential exposure. The presence of positive findings may be useful in demonstrating underlying conditions or identifying stigmata of some toxic exposures. The interval between exposure and the time of examination may yield a normal examination despite significant workplace exposure.

**Laboratory studies**

The laboratory investigation should be geared toward the proper evaluation of the expressed symptoms and observed findings according to the formulation of a differential diagnostic process rather than limited to studies that only examine a potential toxic cause. Careful consideration should be undertaken before submitting any biologic sample to a laboratory for analysis of the chemical substance that is believed to be responsible for the symptoms. Although the toxicology laboratory may have a role in the evaluation of patients who are exposed to chemical substances, there are many substances that can produce a notable symptomatic response without significant systemic absorption (eg, irritant gases, vapor).

Biologic exposure indices (BEIs) have been established for a few substances that are encountered in the workplace. These indices act as a guide to approximate an exposure at the threshold limit value (TLV; discussed later in article). They are intended to be a marker of exposure at which most workers do not experience adverse health effects. It is not intended to be a marker for documentation of toxicity. Before submitting a blood or urine sample for analysis, BEIs should be consulted to establish the correct sampling procedure. The BEI may specify that the sample should be obtained before, during, or at the end of the work shift. Some sampling can be discretionary or must be performed at the end of a 40-hour, 5-day workweek. Urine sampling also requires that the creatinine concentration fall within the range 0.3 g/L to 3.0 g/L or that the specific gravity is greater than 1.020 and less than 1.030 [2]

Laboratories that offer batteries of toxic elements, sometimes in conjunction with nutritional or mineral elements, should be avoided. One such laboratory describes itself as a “leader in functional medicine laboratory testing and wellness education” and promotes these services to “health-care professionals practicing in the field of complimentary and alternative medicine.” A disclaimer now is cited on reports from some laboratories, indicating that the test results are “not based on data from reference populations and should be used for illustrative purposes only” and have “not been cleared or approved by the U.S. Food and Drug Administration” [3]. The clinician must
beware of the significant limitations of such laboratories. Although hair testing for multiple toxic elements may be appropriate for forensic investigations or epidemiologic studies, it rarely is useful in the proper evaluation of a patient exposed to toxic substances. Hair sampling is subject to technical difficulties and improper or absent standardization. The limitations of hair-testing laboratories were documented in a study that found widely different methods and calibration standards and found an up to a 10-fold variation in reported results among laboratories [4].

**Radiographic studies**

Performing a chest radiograph after an acute high-intensity exposure to pulmonary irritants may demonstrate bilateral infiltrates that represent chemical pneumonitis or pulmonary edema. A chest radiograph may be useful to identify potential underlying pulmonary disease that may make the patient more apt to become symptomatic after exposure in the workplace. A high-resolution chest CT scan produces a specific and useful image that can identify lung parenchymal abnormalities that may not be evident on a plain chest radiograph. When nasal or sinus pathology is suspected, a sinus CT scan may be useful.

**Spirometry**

Properly conducted spirometry in conjunction with measurement of lung volume and diffusion capacity can help to document pulmonary impairment after an inhalational exposure or to establish a diagnosis of underlying pulmonary dysfunction. If abnormal bronchial responsiveness is suspected, a methacholine challenge can be used to establish the presence of nonspecific bronchial hyperreactivity. The criteria for conducting and interpreting the methacholine challenge have been set forth by the American Thoracic Society. [5]

**Exposure assessment**

**Industrial hygiene survey**

An objective assessment of exposure often requires the assistance of an industrial hygiene consultant, who is trained to recognize, evaluate, and control a variety of workplace or environmental factors that may result in adverse health effects. An industrial hygienist consultant can conduct a workplace inspection and determine the actual levels of exposure of chemical substances to workers. The workplace inspection is referred to as an industrial hygiene survey when it is performed at an industrial facility. The same approach in the office environment may be called an indoor air-quality survey. The workplace inspection includes a review of workplace practices; the type and quantity of chemical substances used; engineering controls, such as ventilation; and the appropriate use of
personal protective equipment. When potential exposure must be evaluated, air sampling may be performed to measure specific concentrations of airborne substances. Sampling can be performed at the breathing zone of the worker or in a location at the plant during a specific process. When properly performed, sampling data can provide the most objective data about the intensity and duration of exposure at the workplace. This information can be helpful in assessing a relationship between the patient’s expressed symptoms and perceived exposures at the workplace [6].

Threshold limit values

Interpretation of airborne sampling results that are obtained during an industrial hygiene survey requires a review of established workplace standards or guidelines. To provide guidelines for the control of exposures to chemical substances in the workplace, TLVs have been developed by the American Conference of Governmental Industrial Hygienists (ACGIH). This professional organization includes members from the government, academia, and the industry who are devoted to the promotion of sound industrial hygiene practices. The TLV is an airborne concentration of vapor, gas, or particulate to which “nearly all workers may be repeatedly exposed day after day without adverse effect” throughout a working career. These values are derived from human and animal studies and from practical experience. The TLV is the level at which the worker is protected against the development of illness, irritation, nuisance, and excessive discomfort. Because of individual susceptibility, some workers may experience discomfort when exposed to concentrations at or below the TLV. In some cases, a small percentage of workers could have serious symptoms. A worker who previously was sensitized to toluene diisocyanate (TDI) may experience severe symptoms when exposed to concentrations well-below the TLV.

Although TLVs are the most widely used industrial standards, they do not carry the force of law. Legally mandated exposure limits are established by the Occupational Safety and Health Administration (OSHA) as permissible exposure limits (PELs). The lengthy procedures required to establish PELs have resulted in relatively few standards, compared with the number of TLVs from the ACGIH.

The TLV time-weighted average (TLV-TWA) is the concentration to which a worker may be exposed on a daily basis if he or she works an 8-hour workday and a 40-hour week. Because the TLV-TWA represents an average concentration over the course of the day, it may not be an appropriate standard when airborne concentrations fluctuate significantly because of industrial processes that intermittently produce higher concentrations. In this instance, the short-term exposure limit (STEL) is the appropriate standard. The STEL is the concentration to which the worker should not be exposed for longer than 15 minutes at any time during the workday. Because this 15-minute period concentration is an average, it is possible that a high peak concentration of gas or vapor could produce a symptomatic response. For this reason, a few substances, particularly irritant
gases and vapors, may have a defined ceiling limit. The ceiling value places a limit that may not be exceeded at any time. For irritant gases or vapors, the ceiling limit may be the only relevant TLV. When two or more substances with similar toxicologic properties are present at the same time, the additive effects must be taken into account by reducing the TLV for each substance proportionately. If two irritant gases each have a TLV of 50 ppm and are present in equal concentrations, the adjusted TLV for each gas is 25 ppm.

Threshold limit values should not be used as a “cut point” for determining whether an exposure is safe or toxic. The ACGIH developed the TLVs to be used by industrial hygienist consultants for the control of potential health hazards and not for the purpose of “proof or disproof of an existing disease or physical condition” [7].

**Material safety data sheets**

The OSHA Hazard Communication Standard requires all employers to provide material safety data sheets (MSDSs) to workers who use toxic materials at the workplace. MSDSs provide information regarding the safe use of the chemical product, such as proper protective gear, proper handling, and procedures to follow in the event of an accidental spill or release. The MSDS also contains a listing of the specific chemical substances that are contained in the product. The identity of the substances to which a worker is exposed may be important information to consider when confronted with a symptomatic patient [8]. Information about the toxicologic properties of the substances then can be obtained from reliable sources. Although a description of health hazards is included in the MSDS, the information is usually a general listing of symptoms and potential medical conditions that is intended to make the worker aware of the medical complications that could occur after overexposure to the product. Workers often present to physicians with the health-effects information from a MSDS after matching nonspecific symptoms to their own symptoms and concluding that poisoning has occurred. Although the patients’ concerns should be addressed, physicians should rely on the formulation of an appropriate differential diagnosis and should not rely on the MSDS for diagnostic assistance. The described effects of an MSDS rarely are placed into the context of a dose–response relationship and provide little diagnostic help. Use of the health-hazard information of an MSDS has been criticized as an impediment to proper medical evaluation by physicians, and because of ambiguity, the proper diagnosis may be delayed. [9]. In some cases, the MSDS information may be incomplete. It was found that asthma was indicated as a potential hazard of TDI exposure in only 50% of MSDSs in a random survey of 30 manufacturers [10]. The reported ingredients of some MSDSs may be inaccurate if the MSDS is not current. The ingredients may be estimated or may not be stated accurately [11]. Some ingredients are exempt from inclusion in MSDSs because of their nonhazardous status or proprietary confidentiality. These shortcomings should provide the impetus to consult a reliable source of toxicologic information, such as a regional poison control center.
Toxic effects of irritants

Anatomic functional considerations

The upper respiratory tract provides filtration and removal of some noxious substances from the ambient air. As air transits the nasal, pharyngeal, and laryngeal structures, it is conditioned and humidified. It also is routed through the nose, flowing past nasal hairs that trap large particles. As the air continues through the nasal passages, the pattern of flow changes from laminar to turbulent flow. Because of the small cross-sectional area of the nose, relatively large concentrations of particles or water-soluble substances are deposited. At the same time, the air flowing over the nasal mucosa is sampled by the receptors of the olfactory and trigeminal nerves, which provide information regarding the presence of possible noxious agents in the environment. The location and function of the structures of the upper airway make them first-line defenses against exposures to airborne substances and a target for adverse effects. The upper airway is the focus of symptomatic complaints during or after many occupational or environmental exposures. Common manifestations of exposures to many gases, vapors, and particulates include the nonspecific presentation of nasal congestion, rhinitis, pharyngitis, or laryngitis. Corresponding ocular complaints often accompany these manifestations. Development of such symptoms is not specific to an exposure to chemical substances and may describe an allergic exposure, recent development of an upper respiratory infection, vigorous exercise, or cigarette smoking. Workers often believe that an irritant response is an indicator of an allergic response [12].

Larger particles that are trapped in the mucosal surfaces of the upper airway are cleared through the action of mucociliary transport. Particles that are transported anteriorly may be expelled with sneezing, swallowed, or expectorated when transported posteriorly into the pharynx. This mechanism accounts for exposure and the development of toxicity to many fumes and particles such as lead, manganese, and other heavy metals that are too large to be carried into the lung from the upper airways.

Odor

Although not all potentially toxic substances produce the perception of odor (eg, carbon monoxide), most substances that adversely affect the respiratory tract are irritants that produce an odor. Because odor is often the first-recognized sensation in the setting of a toxic exposure, it is important to understand the role of odor in the range of possible responses.

Odor perception is often the sentinel event that indicates to the worker that a potentially toxic exposure has occurred. In the industrial setting, odors may be a normal part of the work environment or may be an indicator of a leak, spill, or malfunction of a respiratory protective device. Although the experience of an odor often alerts a worker to the presence of a chemical substance, it may or may
not be associated with toxicity. Even at concentrations too low to produce a physiologic effect, many chemicals can produce a perceptible, sometimes unpleasant odor that may create or validate a belief that a toxic exposure has occurred (Table 1). The association between illness and odor is common, as illustrated by a study in which 60% of college students reported unpleasant symptoms when presented with odors of automobile exhaust, paint, new carpet, or perfume [13]. The modification of perception caused by expectation has been demonstrated in studies of subjects who reported significantly greater symptoms when they were told that they were being exposed to an industrial solvent but reported relatively few symptoms when informed that the same chemical was a natural extract [14]. Although some odors universally are regarded as unpleasant, learned associations between odor quality and symptom onset is a fundamental behavioral response. When an animal is presented with a novel flavor on a single occasion and illness then is induced with lithium or apomorphine, the animal remembers the experience and avoids further contact with the offending substance, even though the odor itself did not induce the illness [15]. This phenomenon can result in undesirable consequences for patients undergoing radiation and chemotherapy when nausea and vomiting is paired coincidentally with the presence of odor from foods or other sources [16,17]. The same learning paradigm also seems to be responsible for some reported symptoms among workers in industrial settings who experience odors in the presence of illness [18,19]. The presence of odor may engender a psychologic response resulting from aversive conditioning and, in some cases, produce panic-like symptoms [20] or episodes of dizziness, nausea, and weakness [21], even when the exposure is well below a concentration that could produce a toxic response.

Odor is perceived by two neural pathways: the trigeminal (fifth cranial nerve) and the olfactory nerve (first cranial nerve). Stimulation of the trigeminal nerve endings in the nasal mucosa produces the nonspecific sensation of irritation or pungency. This perception is referred to as common chemical sense (CCS) and may trigger sneezing, rhinitis, tearing, or the perception of irritation. The concentration required to produce this effect varies but seems to depend on the physical and chemical properties of the substance. Chemically reactive substances and water-soluble chemicals tend to produce a greater sense of

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Odor threshold (ppm)</th>
<th>Odor character</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetone</td>
<td>140</td>
<td>Sweet/fruity</td>
</tr>
<tr>
<td>Styrene</td>
<td>0.15</td>
<td>Sharp/sweet</td>
</tr>
<tr>
<td>Toluene</td>
<td>1.74</td>
<td>Sour/burnt</td>
</tr>
<tr>
<td>Trichloroethylene</td>
<td>0.21</td>
<td>Aromatic</td>
</tr>
<tr>
<td>Trichlorotrifluoroethane</td>
<td>135</td>
<td>Sweet</td>
</tr>
<tr>
<td>Xylene</td>
<td>0.27</td>
<td>Sweet</td>
</tr>
</tbody>
</table>

pungency. In the case of solvent exposure, it has been shown that the sensation of pungency is dependent on the length of the carbon chain, in which the smaller molecules produce a greater perception of pungency than do larger molecules. This effect can account for a greater than 1000-fold perceptual difference between an 8-carbon molecule and a 1-carbon molecule [22,23]. The subtle odor of large molecules is contrasted to the pungent sensation associated with formaldehyde.

In contrast to the nonspecific CCS, the olfactory nerve gives rise to specialized receptors of the olfactory bulb that is located in the superior portion of the nasal cavity, forming two small patches of olfactory epithelium. The interaction between volatile chemicals and these specialized receptors is not well understood. Many substances simultaneously can stimulate the CCS and olfactory receptors, although some substances (eg, carbon dioxide) do not stimulate olfactory receptors but can produce sensory stimulation of the CCS only at high concentrations [24].

After a few minutes of odor perception, olfactory sensation is extinguished rapidly [25], whereas sensory irritation tends to be persistent. This effect was demonstrated in a study of subjects who rated the intensity of perceived irritation and odor during exposure to a mixture of 22 volatile organic compounds (VOCs) at a total concentration of 25 mg/m³. These subjects experienced rapid fading of odor perception but the intensity of pungency, and associated symptoms of headache or drowsiness persisted [26].

**Irritation**

In the absence of objective findings, the distinction between odor and irritation is usually subjective. Sensory irritation does not necessarily imply injury, although it often is perceived as undesirable, annoying, or noxious. Whether or not injury has occurred, however, sensory irritation is a common perception that may prompt medical evaluation for a possible toxic exposure. Examples of irritant gases and vapors are detailed (Box 1).

Low concentrations of acetic acid may produce only a subtle but recognizable odor of vinegar by way of the olfactory nerve, whereas higher concentrations initiate stimulation of the trigeminal nerve and produce undesirable symptoms of irritation. Substances such as acetic acid produce an irritant sensation by inducing the release of several neuropeptides, including substance P and the calcitonin gene-related peptide, from peripheral trigeminal nerve terminals. This neurologic response to sensory irritation produces the undesirable symptoms of ocular and nasal irritation with associated tearing, sneezing, and rhinitis. Local release of histamine and other inflammatory mediators can cause reflex bronchial reactivity [27]. It is believed that some irritants, such as diesel exhaust, can produce nasal hyperresponsiveness when neuropeptide release is accompanied by the presence of histamine [28].

The subjective perception of irritation can be affected by a variety of circumstances [29]. Persons with a history of atopy often report more symptoms.
after exposure to irritant substances than do persons without atopy [30]. The subjective response to irritants also is dependent on gender: Women report higher rates of symptoms than do men [31]. Expectation and previous experience with odor or associated irritation also has a role in the production of symptoms. A single low-level exposure to the odors of construction materials in an indoor office space may result in numerous complaints and generate multiple medical visits by office workers, whereas the construction workers who used the same materials in the same office space (and who experienced substantially higher exposures) have no symptoms. This disparity of perception also is illustrated by the adding to foods of horseradish, chili peppers, onions, and citrus fruits, which, although irritants, are regarded as components of a pleasant culinary experience; in contrast, the same level of sensory irritation from an occupational exposure to chemicals at the workplace may be perceived as unpleasant or dangerous, regardless of whether the exposure exceeds permissible standards.

Although odor perception is alleged to have a role in the exacerbation of asthma, it seems that sensory irritation is a more significant factor. Asthmatics have been described as responding with a symptomatic exacerbation when exposed to the odor of insecticides, perfumes, cleaners, paint, and cigarettes [32]. When challenged with cologne, subjects with asthma experienced a decline of 18% to 58% below their baseline forced expiratory volume in 1 second. Although odor has been identified as the important variable in these cases, concentrations were not assessed. The same response occurs in anosmic subjects and in subjects wearing nose clips [33], suggesting that sensory irritancy may be a greater factor than odor perception alone.

Attempts to objectively measure the irritant response often rely on subjective reports. When exposed to a concentration of 5 to 8 mg/m$^3$ of volatile organic
compounds, subjects complained of unpleasant mucous membrane irritation [34,35]. As the concentration was increased to 25 mg/m³, subjects reported additional symptoms of headache, drowsiness, fatigue, and confusion [36]. At concentrations approximate to industrial exposure levels of N-decane, which varied from 40 to 400 mg/m³, subjects reported dose-dependent symptoms of mucosal irritation [37].

Investigations which sought to objectively measure upper airway mucosal inflammatory responses at low levels of exposure encountered technical difficulties and mixed results. Koren attempted to measure nasal inflammatory responses to a mixture of 22 VOCs at a concentration of 25 mg/m³ in test chambers by measuring neutrophil concentrations in the nasal lavage fluid of nonsmokers without allergies. It was not clear if the increased levels of neutrophils resulted from an inflammatory response to the VOCs or from the large variability among subjects and an unexpectedly high preexposure neutrophil level in the lavage fluid [38]. Electrophysiologic methods also have been used to correlate perceptual descriptions of irritation with an objective measure of nasal mucosal potential or cortical event-related potentials.

**Injury**

The potential for injury to the lower respiratory tract by irritant gases and vapors depends on the intensity (concentration) and duration of exposure. The physical and chemical properties of the substance are also determinants of the magnitude and location of injury. Water-soluble substances, such as ammonia, chlorine, mineral acids, and formaldehyde, rapidly dissolve into the moisture of the mucosal surfaces of the eyes and upper airways (Box 1). The major effect may be limited to the eyes and the upper airways and spare the lungs from significant injury. An overwhelming exposure to such a substance or an exposure from which the worker cannot escape results in pulmonary injury. In contrast, gases or vapors that are relatively water-insoluble, such as phosgene and some oxides of nitrogen, may produce a minimal ocular or upper airway response as an indicator of potential significant pulmonary injury. The pulmonary injury may be manifested hours later by increasing cough, dyspnea, or possible pulmonary edema.

After a single high-intensity exposure to an irritant gas, persistent lung injury may lead to symptoms and findings similar to asthma. This condition has been called reactive airway dysfunction syndrome (RADS) [39], and it continues to generate controversy regarding proper diagnostic criteria and projected prognosis [40]. Patients who qualify for this diagnosis must have persistent asthma-like symptoms (ie, cough, wheezing and dyspnea, with objective evidence of nonspecific bronchial hyperresponsiveness without a previous history of pulmonary disease). An accurate diagnosis is difficult when the exposure is characterized poorly, an accurate medical history cannot be verified, or the patient has underlying atopy or a history of smoking. The concept of low-level RADS also has been proposed [41]. Because this theory contradicts the dose–response relationship, it seems unlikely that a toxicologic mechanism (ie, irritation) is responsible for the
observed symptoms and findings. It is more likely that most of the reported cases represent preexisting asthma or expressions of an atopic predisposition [42].

The development of a transient exacerbation of underlying asthma after exposure to an irritant gas or vapor is more common than the onset of de novo asthma after exposure to a potential sensitizer or the onset of RADS after exposure to an irritant. A temporary exacerbation of asthma among the 5% to 10% of adults who have this condition [43] is a relatively common response to the nonspecific irritant properties of numerous substances encountered during activities of daily living or in the workplace (eg, tobacco smoke, VOCs emitted from paint and other construction materials, perfumes). The response is dependent on the concentration and irritancy of the substance and the degree of bronchial responsiveness. [44]. A patient with severe asthma may develop an acute symptomatic exacerbation when exposed to concentrations of irritant substances below the established TLVs. The magnitude of an asthmatic response as it correlates with the severity of asthma has been demonstrated with exposure to acid irritants [45]. The nonspecific bronchial response to irritants is diminished if the patient is currently receiving medical treatment for asthma [46]. Because asthmatics frequently experience acute worsening of their underlying asthma after developing an upper respiratory infection, in spite of any potential exposures to irritants, it is challenging for the clinician to determine the etiologic role of an irritant exposure versus the sequella of infection.

In addition to respiratory injury, some gases, vapors, mists, or particulates may be absorbed through the lungs and produce symptoms and findings of systemic toxicity. Most of the hundreds of organic solvents commonly used in industry in the form of paints, cleaners, and adhesives are can producing respiratory irritation and depression of the central nervous system, resulting in concomitant dizziness, confusion, or loss of consciousness. Some solvents have unique toxicologic features and may produce a variety of adverse effects. N-hexane is associated with peripheral neuropathy, and benzene may cause suppression of bone marrow or acute myelogenous leukemia. A discussion of the varieties of potential toxic exposures can be found in several texts devoted to the practice of medical toxicology [47, 48].

Summary

The evaluation of a potential toxic exposure requires a detailed patient evaluation in addition to consideration of the specific chemical substance, route of exposure, duration and intensity of exposure, and documentation of the pathologic consequences.

References


