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Persistent effects of chlorine inhalation on respiratory health

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Abstract

Chlorine gas is a toxic respiratory irritant that is considered a chemical threat agent because of the potential for release in industrial accidents or terrorist attacks. Chlorine inhalation damages the respiratory tract, including the airways and distal lung, and can result in acute lung injury. Some individuals exposed to chlorine experience a full recovery from acute injury, whereas others develop persistent adverse effects, such as respiratory symptoms, inflammation, and lung-function decrements. In animal models, chlorine can produce persistent inflammation, remodeling, and obstruction in large or small airways, depending on species. Airways with pseudostratified epithelium are repaired efficiently, with surviving basal epithelial cells serving as progenitor cells that repopulate the complement of differentiated cell types. Distal airways lacking basal cells are repaired less efficiently, leading to chronic inflammation and fibrosis at these sites. Persistent chlorine-induced airway disease in humans is treated with asthma medication to relieve symptoms. However, such treatment does not ameliorate the underlying disease pathogenesis, so treatments that are more effective at preventing initial development of airway disease after irritant gas exposure and at reversing established disease are needed.

Keywords

chlorine; chemical threat agent; small airway disease; bronchiolitis obliterans

Chlorine as a chemical threat agent

Chlorine is a reactive gas used in a variety of industrial processes, including the production of plastics, solvents, paper products, and purified drinking water. Chlorine is considered a chemical threat because of the large amounts that are produced and transported in the United States, its ready availability, and its acute toxicity. Chlorine is highly toxic by inhalation, and toxic exposures to humans have occurred from both accidental and intentional releases of chlorine. Chlorine poisoning can occur in household or swimming pool accidents involving

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Conflicts of interest

The authors declare no conflicts of interest.

cleaning supplies and disinfectants.[1,2] Toxic exposures have also occurred through accidental chlorine release in industrial settings.[3] Large amounts of chlorine are transported by rail to end-use sites distant from production facilities. Because of this, chlorine transported in rail cars represents the most serious threat for human casualties from accidental release. Lethal chlorine spills from rail cars occurred in 2004 in Texas and in 2005 in South Carolina. In the Graniteville, South Carolina accident, nine people died and 72 were hospitalized.[4] Chlorine has been used as a chemical weapon, first in World War I and more recently in the Iraq war and the Syrian civil war.[5] The most serious domestic threat for intentional chlorine release likely involves attack on industrial storage facilities or rail cars during transport.

Acute effects associated with high-level chlorine exposure in humans are dyspnea, airway obstruction, cough, cyanosis, nausea, vomiting, and loss of consciousness.[6–8] The lung is a main target of chlorine toxicity, but the eyes, skin, and heart may also be affected. The initial injury that occurs in the lung following chlorine inhalation is damage to the respiratory epithelium, which is a common pathological manifestation caused by inhalation of many pulmonary toxicants. Chlorine is highly reactive and is effectively scrubbed by the respiratory tract at lower concentrations.[9] Lower chlorine doses will produce only airway injury; higher doses will produce both airway and alveolar injury, including pulmonary edema. Subsequent pulmonary symptoms and pathophysiologic events result to a large degree from the loss of respiratory epithelial barrier function. Resolution of chlorine-induced lung injury is dependent on repair of the respiratory epithelium, and normal repair is critical to prevent long-term pulmonary pathology that can occur following acute injury. Here we review the evidence for persistent adverse health effects of chlorine on the respiratory system in humans, the progress in modeling these effects in animals, and the prospects for treatment of persistent chlorine-induced lung disease.

Persistent effects of chlorine exposure in humans

The largest-scale human exposures to chlorine occurred during World War I, when the gas was used as a chemical weapon. Summaries of World War I follow-up studies involving military veterans are available in the chlorine review literature;[10,11] opinions differ, but collectively the inference is that those exposed to chlorine gas experienced a high incidence of acute obstructive respiratory disease but a low prevalence of long-term chronic sequelae. While these studies represent an initial documentation of acute, high-concentration residual effects, there were inherent difficulties in linking chronic disease states to chlorine exposure. The majority of the retrospective war gas studies lacked classifiable chlorine-only exposure data, uniform physical diagnostic criteria, and pulmonary function testing. In addition, the effects of confounding factors, such as smoking status and the presence of tuberculosis, influenza, and pneumonia, were difficult to assess.

Numerous sporadic chlorine exposure incidents from accidental releases in industrial, transportation, or household settings have been documented.[3] Reports from such civilian chlorine disasters have often stated that the victims were generally able to fully recover or presented with relatively normal lung function at longer times after exposure.[8,12] Therefore, it has been said that most people acutely exposed to chlorine make a full recovery without

residual health effects.[13] For example, an epidemiological study of a community acutely exposed to chlorine gas found no pulmonary disorders attributable to exposure, although modeling of exposure proved difficult and was assessed as distance to spill only.[12] However, other studies have suggested long-term pulmonary abnormalities following acute chlorine exposure, including airway obstruction and hyperreactivity.[14–17]

In 1985, the term *reactive airways dysfunction syndrome* (RADS) was coined to describe a condition in which previously healthy individuals developed an acute-onset irritant-induced asthma that frequently lasted for years following a single high-dose irritating gas or fume exposure.[18] Although some early reports suggested that chlorine gas exposure did not lead to RADS, later studies of chlorine-induced RADS began to appear that included objective measures of pulmonary function and airway reactivity. Long-term effects of chlorine inhalation have been studied in the context of RADS/acute irritant-induced asthma. A study of patients with acute irritant-induced asthma (over half of whom had disease that was attributed to chlorine exposure) found that respiratory symptoms, such as wheezing and dyspnea, continued to be present when assessed at a mean duration of 12 years after diagnosis.[19] These patients had impaired lung function evidenced by reduced forced expiratory volume in 1 s (FEV_1), which did not improve over the course of the follow-up period. Pathophysiological studies have suggested that chlorine exposure can result in airway fibrosis and that patients with acute irritant-induced asthma caused by chlorine exposure may have a greater extent of airway fibrosis than individuals with other types of asthma or without asthma.[14,20–22] Airway fibrosis in acute irritant-induced asthma has been detected in bronchial biopsies. On the basis of results from other irritant gases and in animal models of chlorine inhalation (discussed below), small airway pathology and bronchiolitis obliterans seem possible in humans, but these have neither been supported nor ruled out by the available evidence. Increased inflammatory cells and inflammatory mediators have also been observed in the lungs of patients with acute irritant-induced asthma stemming from chlorine exposure.[19,21–23]

On January 6, 2005, a train derailment and 54,422-kg chlorine gas spill occurred in the cotton mill town of Graniteville, South Carolina.[24,25] This resulted in the largest U.S. civilian population ever exposed to chlorine.[26] Following the accident, nine people died immediately, 72 were hospitalized,[27] several hundred people immediately became sick and received medical care, and thousands were exposed.[28–32] An exposure registry was developed, and community health screenings were provided in 2005–2007.[29,32,33] Using validated plume models, individual chlorine exposures were estimated.[26,34,35] Over the 3 years following the chlorine release, rates of hospitalization and emergency department visits for ambulatory care–sensitive conditions increased significantly in the Graniteville population compared with a nearby population not exposed to chlorine.[36–38] In the year following the accident, Graniteville millworkers had significantly reduced FEV_1, and the prevalence of millworkers with accelerated FEV_1 decline was increased.[39]

Persistent effects of chlorine exposure in animal models

Because of the challenges in understanding the persistent effects of chlorine exposure in humans, animal studies, in which chlorine exposure levels and analysis end points can be

experimentally controlled, have been pursued. Chlorine inhalation injures the cells lining the respiratory tract, and this damage must be repaired to reestablish normal lung structure and function. Long-term impairment in lung function following irritant gas exposure is likely to be caused by the failure of repair processes to return the structure of the lung to its normal state. Hence, studying the repair of the respiratory tract after chlorine inhalation is instructive for understanding how persistent disease may develop and for developing therapeutic interventions. Damage to the airway epithelium is a common manifestation of chlorine lung injury that has been observed in multiple animal models. At low doses of chlorine (e.g., 100 ppm for 5 min), functional alterations can be observed in the absence of gross changes in airway histology, but increased protein leak under these conditions indicated some type of epithelial damage, such as impaired barrier function, in the absence of frank cell death.[40] Widespread death and sloughing of airway epithelial cells has been a consistently observed feature in models utilizing higher doses of chlorine (240–1500 ppm for 5–60 min) that result in acute lung injury.[41–47] Depending on the dose, chlorine can damage the entire extent of the airway epithelium, from the nasal passages to the terminal bronchioles.[47] The process by which the pseudostratified epithelium in larger airways is repaired after chlorine injury has been examined in detail in mice.[44,48,49] Chlorine doses that produce acute lung injury (240 ppm for 60 min or 350 ppm for 30 min in these studies) result in the death and sloughing of most epithelial cells from the pseudostratified epithelium, including virtually all club and ciliated cells. Basal epithelial cells that survive the exposure spread to cover the wounded area within a day after exposure. The basal cells act as progenitor cells to carry out repair; they undergo a burst of cellular proliferation during the period of 2–4 days after exposure, followed by a period of differentiation 5–10 days after exposure to restore a pseudostratified epithelium that again contains basal, club, and ciliated cells. The overall process is similar to that observed following inhalation of other irritant gases, such as sulfur dioxide,[50] and is likely to be the main process by which the airway epithelium is repaired in human lung, as the pseudostratified epithelium in humans penetrates for multiple generations of branching into smaller bronchioles. Repair of simple epithelium in smaller airways has not been investigated in detail following chlorine exposure, but is likely to involve surviving club cells that act as progenitors to restore the epithelium, as has been observed in other injury models.[51,52]

Differences in the responses of inbred mouse strains to chlorine inhalation have been observed, indicating that repair capacities are to some extent under genetic control. Some inbred strains of mice (e.g., C57BL/6 and FVB/N) have a sparse complement of basal cells in distal trachea, main stem bronchi, and lobar bronchi, and these mice exhibited impaired repair characterized by a failure in airway re-epithelialization.[44,48,49] These mice had airway inflammation characterized by macrophages and neutrophils, and they developed airway fibrosis at these sites 7–10 days after exposure. Mice that developed airway fibrosis exhibited lung function abnormalities, including increased baseline lung resistance and airway hyperreactivity to inhaled methacholine.[48] This was in contrast to A/J mice, which had more abundant basal cells at these sites and showed efficient epithelial repair, lack of fibrosis, and return to normal lung function, even though the initial chlorine injury appeared equivalent in all three strains.[48] The findings are consistent with older literature showing delayed mortality in mice exposed to chlorine and bromine.[53] Although the injured

epithelium in A/J mice was repaired rapidly and fibrosis was prevented, these mice developed persistent lung abnormalities following chlorine exposure, including abnormal distribution of airway epithelial cells and chronic inflammatory cell infiltration.[54] Another model using A/J mice exposed to 800 ppm chlorine for 5 min reported airway remodeling; most aspects of this appeared transient, but a modest increase in airway collagen deposition was observed 10 days after exposure.[55]

Chlorine exposure in other species has also been shown to lead to long-term changes in lung structure and function. Rats exposed to 1500 ppm chlorine for 5 min developed increased baseline lung resistance and airway hyperreactivity.[41] In most animals, these returned to baseline values by 7–14 days after exposure, but in a subset of animals (13–25%), abnormal values persisted for at least 90 days. These animals also developed pulmonary inflammation, as indicated by increased neutrophils and lymphocytes in bronchoalveolar lavage fluid. As outbred Sprague-Dawley rats were used in this study, these findings may also suggest a variability in responses that is under genetic control. Changes in airway structure as revealed by light microscopy were generally resolved by 14 days after exposure. In contrast, chlorine exposure in dogs produced more profound, long-lasting changes in lung structure. Spontaneously breathing dogs subjected to whole-body chlorine exposure developed chronic airway inflammation with bronchiolitis obliterans lesions in small airways in which the airway lumen could become completely occluded.[47] The airway pathology led to abnormalities in the lung parenchyma with alternating areas of emphysema and atelectasis. This disease in some cases was progressive and led to death of animals between 15 and 193 days after exposure. The respiratory tracts of mice and dogs differ in two important ways that may explain the differences in the site of persistent lesions. First, mice are obligate nose breathers with extensive nasal epithelium surface area, and this may provide some scrubbing of chlorine, which limits the penetration of the toxic gas to the more distal airways. Thus, there may be less injury at the bronchiolar level in mice compared with dogs. Second, in mice, pseudostratified epithelium with basal cells is limited to the more proximal airways and does not extend beyond the lobar bronchi. By contrast, in nonrodent species, basal cells extend deeper in the lung to smaller bronchi. Basal cells appear to be relatively resistant to chlorine,[44,46] although it is not clear whether they are protected merely by their position beneath the other luminal cell types or whether this results from some unique physiological properties. Because of this, surviving basal cells could carry out efficient repair in proximal airways, but injured airways distal to the point where the pseudostratified epithelium stops would be repaired inefficiently, leading to inflammation and fibrosis in smaller airways.

Insights from other inhaled toxicants

Long-term adverse effects on the respiratory system have been observed following exposure to other pulmonary toxicants, and information related to these other agents may provide insights into the types of persistent abnormalities that can occur, as well as the underlying mechanisms. Here, we review persistent effects following inhalation of methyl isocyanate and sulfur mustard, two toxic gases for which information from large-scale human exposure is available. Chlorine, methyl isocyanate, and sulfur mustard are all highly reactive, produce adducts with a variety of biomolecules, and can cause direct injury and cellular death. Chlorine and methyl isocyanate are potent irritants and strong electrophiles. Methyl

isocyanate is an alkylating agent that reacts preferentially with guanine bases to damage DNA, but it can also alkylate a variety of other cellular components, including RNA and proteins. The three compounds have large differences in aqueous solubility (methyl isocyanate > chlorine > sulfur mustard), which will affect the sites of deposition in the respiratory tract following inhalation. Although the mechanisms of producing cellular death differ among the compounds, there is likely to be some overlap in lung pathology that results from killing of epithelial cells that line the respiratory tract.

Hundreds of thousands of people were exposed to methyl isocyanate as a result of an accidental release in Bhopal, India in 1984. Long-term follow-up of this population was difficult, but some evidence was obtained for persistent effects, such as respiratory symptoms, lung function impairment (including both obstructive and restrictive changes), inflammation, and histological abnormalities (including airway inflammation and fibrosis).[56–58] Animal studies have shown long-lasting effects of acute methyl isocyanate exposure on airway structure.[59–64] Persistent inflammation of the airways was observed, as were abnormal epithelial repair and fibrosis that obstructed the lumen of the airways. The location of obstructive airway fibrotic lesions differed by species. In mice, these were restricted to the trachea and major bronchi,[59,60] but in rats and guinea pigs, they were prominent in bronchioles.[61–64] In rats, bronchiolar fibrosis persisted for a year after exposure, the longest time examined, which raised the possibility that this represented a permanent change in the structure of the respiratory tract.[62] In rats and guinea pigs, methyl isocyanate exposure led to pulmonary function abnormalities that included airflow limitation, lung hyperinflation, and air trapping,[65, 66] which was consistent with the small airway disease observed histologically.

During the Iran–Iraq war, Iranians were exposed to sulfur mustard via Iraqi attacks. Many individuals who survived acute sulfur mustard exposure developed long-term decrements in pulmonary function, which persisted for years after exposure.[67–69] High-resolution computed tomography showed a high percentage of cases with air trapping, consistent with small airway disease.[67,70,71] Studies involving analysis of biopsies revealed that bronchiolitis obliterans was a common persistent histological abnormality in these patients.[67,69,71] Information on long-term effects in animal models is limited, but a recent report documented the development of bronchiolitis obliterans lesions in rats exposed to sulfur mustard.[72] Overall, these results suggest a similar type of persistent disease following inhalation of methyl isocyanate, sulfur mustard, and chlorine and indicate that small airway disease, including bronchiolitis obliterans, is a common sequela of toxicant exposures that produce epithelial injury to the bronchioles.

Treatment: current options and future prospects

Humans exposed to high doses of chlorine can develop acute lung injury characterized by pulmonary edema, bilateral infiltrates on chest X-ray, hypoxemia, and respiratory failure.[27] Exposure to lower doses of chlorine can predominantly produce airway injury and obstruction without development of acute lung injury. Treatment for acute lung injury induced by chlorine inhalation includes supportive care, such as oxygen administration and mechanical ventilation. Although no drugs are approved specifically for the indication of

chemical-induced acute lung injury and/or airway obstruction, victims of chlorine poisoning are typically treated for acute effects with multiple drugs approved for other lung diseases.[27] These include systemic and inhaled corticosteroids as anti-inflammatory measures, adrenergic and anticholinergic bronchodilators to ameliorate airway obstruction, and nebulized sodium bicarbonate, which is intended to neutralize the acidic effects of chlorine in the respiratory tract. Therapeutic strategies for persistent chlorine-induced lung disease can be focused on postexposure treatment to prevent the development of persistent disease or on treatment that starts once persistent disease is established. Preventative treatment studies have been performed in rat models. Treatment with the corticosteroid dexamethasone for 7 days after chlorine exposure inhibited inflammation and improved lung function.[73] Chlorine-exposed rats treated with antioxidant therapy showed reduced airway remodeling and airway hyperreactivity 7 days after exposure.[74] Chlorine-exposed dogs developed inflammatory bronchiolar lesions that progressed to bronchiolitis obliterans with intraluminal fibrosis, but no treatment was tested in this study.[47] A recent publication reported human clinical cases of inflammatory bronchiolitis obliterans lesions with incipient fibrosis of unknown causes that were effectively treated with corticosteroids.[75] If such lesions develop in human lungs after chlorine exposure as in the animal model, then corticosteroids may represent a possible treatment that could be tested to prevent the development of persistent chlorine-induced lung disease. In humans, recommended treatment for RADS/acute irritant-induced asthma once established is similar to that for asthma generally (i.e., bronchodilators and systemic corticosteroids for management of acute exacerbations and inhaled corticosteroids with bronchodilators if necessary for chronic maintenance therapy[76]). However, patients treated with these agents can continue to exhibit abnormal lung function.[19,21–23] Thus, these measures may control symptoms, but do not appear to reverse or ameliorate the underlying disease pathogenesis.

Conclusions

Accidental exposures to chlorine, although sporadic, are not uncommon. Concerns also remain that chlorine may be released in warfare and terrorist attacks. Acute effects have been well characterized and may include dyspnea, hypoxemia, pneumonitis, and pulmonary edema. Following recovery from acute chlorine injury, persistent effects may be observed in some individuals. More information is needed to fully understand the types of persistent effects that chlorine can have on the respiratory system, but evidence to date indicates that these primarily involve airway disease. Animal models indicate the development of airway injury, inflammation, impaired repair, and airway remodeling, including fibrosis, but additional models are needed that better represent persistent disease in humans. Little information is available about the actual benefits of potential treatments (e.g., bronchodilators and corticosteroids), so more research is needed in this area, both in preventing development and in treating or reversing established disease. A chronic inflammatory process in injured airways appears to be a hallmark after chlorine exposure, so anti-inflammatory measures during critical postexposure windows may represent a possible therapeutic strategy to prevent the development of persistent chlorine-induced lung disease.

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