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REVIEW ARTICLE

Fluoropolymer-associated illness

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Context: Isolated outbreaks of respiratory illness associated with fluoropolymer-containing products, such as waterproofing agents and sealants, have occurred for many years in many different countries. Despite this, an assured mechanism of illness is not defined, representing a barrier to the prevention of future occurrences. *Objective*: To discuss the epidemiology of the respiratory illness outbreaks, proposed mechanisms of toxicity and clinical outcomes from exposure to these products. *Methods*: We performed a literature review using OVID Medline (January 1946 through December 2012) and PubMed (January 1950 through December 2012) using the search terms "fluoropolymer", "fluorochemical", "leather proofing", "leather protectant", "weatherproofing agent", and "waterproofing agent". Bibliographies of identified articles were screened for additional relevant studies, including non-indexed reports. *Results*: Fluoropolymer-associated respiratory illnesses often resemble polymer fume fever: acute respiratory symptoms predominate and are accompanied by flu-like symptoms. Outbreaks occasionally follow marketing of a new or reformulated product. Treatment with basic and supportive measures is sufficient in many cases, including fresh air and supplemental oxygen. Inhaled beta-2 adrenergic agonists and corticosteroids have been used. Toxicity may result from the fluoropolymer itself or the solvent in which it is delivered. Factors which may influence toxicity include fluoropolymer particle size, emission rate, methods of application, environmental conditions, and personal health. *Conclusion*: Exposure to fluoropolymer-containing waterproofing agents can cause lung injury and usually produce abrupt onset of respiratory and flu-like symptoms. Most victims improve with supportive care and supplemental oxygen. Serious outcomes, including acute respiratory distress syndrome and death, are uncommon. Proprietary information on the exact composition of most fluoropolymer-containing products is often unavailable, and this hinders identification of an exact cause of disease. The etiology is most likely multifactorial. Future research should focus on determining the exact mechanism of illness and establishing safe exposure limits.

Keywords Fluoropolymer; Fluororesin; Fluorochemical; Leather proofing; Weatherproofing agent; Waterproofing agent

Introduction

Fluoropolymers are fluorinated carbon chain polymers and co-polymers that are used in a variety of aerosolized and non-aerosolized household and commercial products as water and soil repelling agents, lubricants, sealants, and leather conditioners.[1,2]

These products have been associated with sporadic outbreaks of respiratory disease, sometimes severe, consisting of cough, shortness of breath, and chest pain and occasionally leading to hospitalization, respiratory failure, acute respiratory distress syndrome (ARDS) and death.[1,3–9] Due to the wide variety of formulations, the intermittent reformulation of these products, the proprietary nature of the compounds, and the fact that product labels and material safety data sheets (MSDS) may not report the presence of a fluoropolymer, it has been difficult to ascertain the specifics of the chemicals involved in these outbreaks to perform studies and determine the reasons for this toxicity in humans.[3]

Aerosolized water repellants generally have three primary components: 1) an organic or inorganic solvent, such as n-heptane, hexane, and petroleum distillates; 2) a propellant, usually carbon dioxide or a short-chain hydrocarbon, such as propane or butane; and 3) a water repelling agent.[6,10] Water repelling agents include fluoropolymer resins, silicon-based resins, and combinations of the two.[6] After application, the solvent vaporizes and the water repelling agent remains on the surface.[11]

One example of product reformulation occurred in the United States in 1994. Prior to this time, waterproofing aerosol formulations commonly included 1,1,1-trichloroethane as a solvent; however, this solvent was removed from the market upon passage of Title IV of the Clean Air Act amendments of 1990.[4,12] Title IV of the Clean Air Act amendments prohibited sale and distribution of nonessential aerosol products that release class I, ozone-depleting solvents, including 1,1,1 trichloroethane, 2,2,4 trimethylpentane, chloroflurocarbons, halons, methyl chloroform, and carbon tetrachloride, and

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required the reformulation of old agents to comply with these regulations by January 1994.[4]

Numerous outbreaks in Asia, Europe, and North America have been reported and multiple theories regarding the mechanisms of toxicity have been postulated. This review will discuss the epidemiology of the outbreaks, proposed mechanisms of toxicity, and clinical outcomes from exposure to these products.

Methods

We performed an extensive literature review using OVID Medline (January 1946 through December 2012) and PubMed (January 1950 through December 2012) using the search terms "fluoropolymer", "fluorochemical", "leather proofing", "leather protectant", "weatherproofing agent", and "waterproofing agent". Both human and animal data were included. Exclusion criteria included non-English literature. These searches yielded a total of 732 citations, which were screened for relevance. Of these, 50 were found appropriate, with the majority of excluded citations either written in a language other than English or found to relate to environmental exposures to fluoropolymers in drinking water or the medical use of fluoropolymers for other applications, such as drug-eluding stents and hernia repair (Supplementary Table 1 to be found online at http://informahealthcare.com/doi/abs/10.3109/15563650.2014.946610). We included all published articles regarding fluoropolymer waterproofing agents and associated respiratory illnesses. We screened the bibliographies of identified articles for additional relevant studies, including non-indexed reports. We also reviewed non–peer-reviewed sources, including books and CDC Morbidity and Mortality Weekly Report publications.

Physical properties

Fluoropolymers, sometimes referred to as perfluorocarbons, are defined by the International Union of Pure and Applied Chemistry (IUPAC) as molecules consisting solely of carbon and fluorine. However, compounds containing other constituents, more accurately described as fluorocarbon derivatives, are also often referred to as fluoropolymers.[13,14] Fluoropolymers comprise a homogenous group of organic plastics that are comprised of strong carbon–fluorine bonds of varying lengths.

Fluoropolymers are ultrafine particles ranging in size from 0.02 to 0.2 μm, although it has been suggested that aging fluoropolymers can aggregate and produce small particle agglomerates measuring up to 15 um.[15,16] This increased particle size has been associated with attenuation of toxicity.[15]

Fluorocarbon liquids, such as those used in the waterproofing and sealing industry are colorless compounds of high density and low viscosity.[14] Because they are not miscible in water and most organic solvents, they are formulated with hydrocarbons (e.g., n-heptane, hexane, and petroleum distillates) for sale and distribution in waterproofing sprays.[6,10]

There have been reports that the proprietary fluoropolymer compounds used in waterproofing products underwent a formulation change following the passage of Title IV of the Clean Air Act amendments, specifically a shift from a fluoroalkane structure to the more toxic fluoroalkene.[12,17] Basic examples of fluoroalkane and its structures appear in Fig. 1. Fluoroalkanes are fluoropolymers that contain only single bonds and are therefore more chemically stable and of lower toxicity than fluoroalkenes, which contain double bonds.[17–20] The fluoroalkenes vary in toxicity, and some are highly toxic, causing acute lung injury and death in both rats and humans.[17,19] Multiple carbon–fluorine bonds further increase the strength and stability of other nearby carbon–fluorine bonds so that longer chain saturated fluorocarbons, such as the fluoroalkanes, are the most chemically stable.[13] Unsaturated fluorocarbons, such as the fluoroalkenes, are much more reactive because the area of the double bond tends to be deficient in electrons.[19,21] This electron deficiency opens the fluoroalkenes up to attack by bases and other nucleophiles, such as fluorine and hydroxyl radicals.[17,19]

The constituents of each fluoropolymer vary, and specific information on the chemical structure and ingredients of proprietary waterproofing agents is often unavailable. The number of carbon atoms in a fluorocarbon determines most physical properties, with the exception of the molecule's heat resistance, or melting point. Longer fluorocarbons with more carbon atoms have higher boiling points, density, viscosity, surface tension, vapor pressure, and refractive index.[15]

Animal studies

From 2005 to 2006, an outbreak of respiratory illness associated with boot sealant product use was reported in animals (pet dogs and cats).[3] Symptoms reported included dyspnea (13/19), cough (3/19), and vomiting (3/19). Of these, four animals required evaluation by a veterinarian and one had a chest radiograph obtained that showed infiltrates. The authors report that one cat met the definition for chemical pneumonitis; however, it is unclear what symptoms this cat had and whether a chest radiograph was obtained. Treatment strategies included bronchodilators (1/19); steroids (1/19); diuretics and anti-inflammatory agent (1/19); and oxygen (12/19). Ultimately, two cats died due to the respiratory failure.

Some experimental studies in animals have investigated clinical signs of respiratory illness and evaluated lung pathology associated with fluoropolymer.[11,15–17,19–20] In 1995, Yamashita and Tanaka exposed female CD-1 mice to various waterproofing aerosols, including one commercial product that was implicated in an outbreak of illness in humans and several fluoropolymer-free products, including one silicone-based water proofing spray.[11] Clinically,

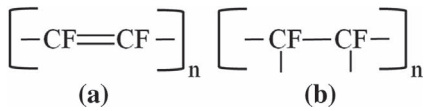

Fig. 1. Basic structure of a fluoroalkene (a) and fluoroalkane (b).

inhalation of the fluoropolymer products caused pneumonia and pulmonary collapse, whereas mice exposed to the non-fluoropolymer–containing products generally had only mild shortness of breath that resolved within 3–5 min. The authors concluded that the fluoropolymer repellents in the waterproofing agent were responsible for the acute respiratory illness, noting that the common component of the waterproofing spray causing toxicity was the fluoropolymer; however, they also concluded that substitution of new "environmentally friendly" solvents in place of the previously used trichloroethane (petroleum solvents such as n-heptane and hexane and industrial gasolines) may facilitate fluoropolymer inhalation by increasing the amount of airborne aerosol.[4,6,7,10,17]

Hubbs et al. performed an experimental study in guinea pigs and rats following a formulation change in a leather conditioner that was associated with a national outbreak of human respiratory illness in 1992.[17] The purpose of their study was to establish whether human disease could have been predicted using toxicity testing in animals and to test their hypothesis that the respiratory illness resulted from a change in toxicity of the fluororesin product, as opposed to being the result of poorly ventilated working conditions, as has been suggested.[22] Following exposure to the new leather conditioner, time-dependent increases in respiratory rate occurred in both rats and guinea pigs. Other clinical effects included pulmonary edema, pulmonary hemorrhage, and death in 6/36 guinea pigs and 5/12 rats. Chemical analysis of the old and new products by gas chromatography–mass spectroscopy (GC/MS) indicated a change from a fluoroalkane to a product containing fluoroalkene, fluorophenyl and/or fluoroalcohol components with some changes in solvent composition.

Mechanisms

Because these products have been associated with periodic outbreaks of respiratory disease, with several case series reporting hundreds of victims, fluoropolymer-related respiratory illness has become a noteworthy public health concern.

Conflicting literature

Review of the available literature on this topic fails to yield a unifying, assured mechanism for the respiratory illnesses seen following exposure to some fluoropolymer-containing commercial products and not others. Any attempt to draw conclusions is further confused by the breadth of contradictory literature on the topic: some sources report an association of respiratory illness outbreaks with a change in particle size[12,16] or emission rate,[12,23] while others report a change in the fluorocarbons,[4,5,23] propellants,[4,5,24] or solvents themselves.[4,5,17] The presence of multiple different reformulations may explain the varying reports. Interactions among different combinations of agents in various reformulations, possibly influenced by a host of personal factors (metabolic activation, smoking, preexisting medical conditions, etc.) may produce new, unanticipated effects; further confounding attempts to ascertain a single mechanism for these periodic respiratory illnesses.[23–25] Although we find the evidence connecting fluoropolymer-associated respiratory illness with a change in fluoropolymer structure (from fluoroalkane to fluoroalkene) most convincing, we suspect that a complex and multifactorial, mechanism of disease exists, heavily influenced by the aforementioned personal factors.

Some authors have suggested various possibilities for these complex disease mechanisms. Yamashita et al. postulated that respiratory sequelae could be the result of a combination of solvent and fluoropolymer particle size. They suggested that newer, more volatile solvents decreased the diameter of the fluoropolymer-containing aerosol particles and thereby increased the amount inhaled when compared with previous formulations.[26]

Direct toxicity of the involved fluoropolymer

One of the leading explanations for the human toxicity seen following aerosolized water repellent exposures focuses on the fluoropolymer as the disease instigating variable. Although we believe in a complex and multifactorial disease etiology, we suspect that a key factor in the fluoropolymer-associated respiratory illness outbreaks is the changes in the fluoropolymer structure discussed in this section.

Both clinical and experimental studies have noted an association with respiratory illness outbreak and reformulation of the commercial products and suggest that introduction of the new fluoropolymer played a central role in the pathogenesis of lung injury[5,11–12,17,21–22,27]; although one case not following a formulation change is reported.[22]

Due to the proprietary nature of these products, specific information about the fluoropolymer structures is not available to the public; however, GC/MS has been performed on some of these commercial products to attempt to gain insight into the structural changes that has accompanied these waterproofing agent reformulations.[12,17] Although these studies did not allow the identification of individual fluorocarbons, information was derived that demonstrated a change in fluoropolymer from a fluoroalkane-containing product to one that contained fluoroalkenes, fluorophenyl, and/or fluoralcohol components.[12,17] The authors felt that this change is sufficient to explain such increases in toxicity, but do overlook the changes in solvent composition that were found on GC/MS analysis, which may be an important contributor to disease.[12,17]

Prior to Title IV of the Clean Air Act amendment-induced product reformulations, human cases of severe respiratory toxicity and death following occupational fluoroalkene exposures were reported.[19] At the time that these cases were reported, fluoroalkenes were available as an industrial chemical, but had not been used in products formulated for public use. The authors, while noting the potentially severe consequences that can result from fluoroalkene exposures, concluded, "Exposure of the general public to fluoroalkenes does not seem to be a significant probability, because these fluorocarbons do not now occupy the marketplace in significant quantities. Should an increase in market penetration of the fluoroalkenes eventuate, much care will have to be exerted to avoid unwanted exposures and additional

toxicologic studies will be required to document more fully the biologic activity of this class of fluorocarbons."[19] Unfortunately, following the more recent illness outbreaks, Clayton acknowledged that these products have been considered "nontoxic" despite the fact that little is known about the fluoropolymers.[19]

Microscopic changes

In an attempt to understand the pathologic changes invoked by waterproofing agents, several experimental studies in rats, mice, and guinea pigs studies included light and electron microscopy images.[15–17,20,29] Primary structural changes included alveolar type I cell necrosis; alveolar type II cell necrosis with resultant impairment of surfactant; direct counteraction of surfactant; alveolar atelectasis and hemorrhage; cilial damage and expansion of alveolar epithelial cell intercellular junctions.[6,11–12,16–17,20,23,30] These changes were felt to be secondary to direct cytotoxicity. Alveolar edema can be delayed, with one study noting delays of 24 h; however in this study, 24 h was the upper limit of surveillance that was undertaken for this finding, so longer latencies could have been missed.[20]

Particle size

Fluoropolymer sprays use small, ultrafine mist particles (0.02–0.2 μm) to help ensure even coating of the product.[23] Because particles less than 10 μm in size are considered respirable, several authors have suggested that the new formulations may increase the amount of fluoropolymer inhaled by decreasing the diameter of the aerosol particles.[11,16,31] Indeed, ultrafine-sized particulates, even nuisance dusts (dusts with low pulmonary toxicity) may produce lung injury by virtue of their ability to translocate across alveolar epithelial barriers, provoking interstitial fibrogenic reactions.[15,32] The reverse situation has been studied, in which increased particle size of some fluoropolymer fumes, was associated with a reduction in toxicity.[15]

The theory that smaller particle size is responsible for increased toxicity was tested under experimental conditions by spraying new and previous formulations of these products and examining particle size.[12] The authors found that the new formulation in their study did not generate smaller particles than the old formulation; however, details of how they determined this were not given.[12]

Emission rate

Some authors felt that reformulation of the products may have led to an increase in the emission rate of particles, ultimately leading to higher concentrations of particle in the atmosphere over a given exposure time. However, two studies of some implicated products under working conditions that determined that the emission rate of respirable particles was lower with the new formulation than with previous formulations (mean = 0.37 mg/s vs. mean = 0.66 mg/s).[12,23]

Particle number

Clinical and experimental findings of some studies suggest that reformulation of the products may have led to an increase in the amount of respirable particles; however study of the spray apparatus under working conditions determined that the number of particles in workers breathing zones was actually lower with one of the implicated, new formulations.[11,14,22–23,33]

Toxicity secondary to solvent

Acknowledging the central nervous system (CNS) effects of some solvents, some authors have also suggested that respiratory illnesses could be attributed to differences in the solvents in the new formulations.[34–35] They cited cases involving exposure to products that used heptanes as a solvent, which they report is more volatile than isopropanol used in old formulations.[21] These authors felt that this increased volatility, independent of the specific fluoropolymer used, was sufficient to allow the product to spread deeper into the tracheobronchial tree where it could induce alveolitis. Others feel that illness could be a result of the solvent itself, as cases of acute pulmonary toxicity following exposure to a hydrocarbon aerosol product that did not contain a fluoropolymer have been reported.[33]

Other authors disagree and highlight scenarios involving petroleum solvents, which cause respiratory illness only after accidental aspiration.[23] They argue that inhalation of aerosol droplets is not sufficient to cause illness. Vernez et al. noted that the solvent composition, new fluoropolymer-containing product, in their study was less toxic than that found in the old formulation, based on a comparison of threshold limits and short-term exposure limits set forth by the Occupational Safety and Health Administration.[23] Hubbs et al. noted a change in the solvent composition to include 2-butoxyethanol and isomers of dipropylene glycol methyl ether, substances not found in the old product.[17] However, the authors dismissed any possible contribution the new solvent may have to the disease process after noting that the systemic toxicity seen with poisoning by these solvents, such as hemolysis and renal lesions, did not occur in the study animals.[17] Additionally intentional inhalation of high concentrations of hydrocarbon for abuse (e.g. "huffing") does not routinely produce acute pulmonary toxicity. In other work, GC/MS analysis of the solvents determined that the solvents were mostly the same in the new product as in the old.[17] Experimental studies have shown that in similar working conditions, solvent concentrations generated by use of the new product were one-half those observed with the old product and consisted of solvents that were previously found to have low toxicity.[23] The authors of this study felt that the solvent could be further ruled out as the illness-inducing factor because the particles reaching the alveoli are "essentially made of nonvolatile material."[23]

Method of application

Many of these fluoropolymer resins are designed to be spread over a surface with a paintbrush or roller; however to save time and reduce amount of product used, they are sometimes applied with a trigger spray.[23] Because this application method could cause increased dispersion of particulate matter into the air, some authors recommend that cans

without propellants should be applied with a paintbrush.[12,23] While strict adherence to manufacturer-recommended application methods is important, many of the reported cases of respiratory illness occurred following use of an aerosolized product, which was used for years prior to the outbreaks in question without incident. Further, other studies have not found differences in particle size, number or emission rate that could be account for toxicity related to this application method.[12,23]

Personal factors

No convincing association between respiratory illness following fluoropolymer resin use and preexisting individual susceptibility factors, such as asthma, allergy, preexisting lung disease, upper respiratory illness or smoking status has been established.[3,4,22]

Lazor-Blanchet and Vernez have suggested that fluoropolymer-related respiratory illness would occur more frequently with occupational use (more frequent or longer duration of exposure) than in home use (infrequent, shorter duration of exposure).[12,23] However, later analysis of national exposure data showed that the majority of exposures resulting in illness, 92% in one series, occur at home.[3,6,8,22,34]

Environmental

Inadequate ventilation in a confined space intuitively seems like a logical contributor to severity of symptoms after use of fluoropolymer aerosols. Fluoropolymers typically lack noxious warning properties such as a pungent odor or upper airway irritation. However, there is no consistent relationship between respiratory symptoms after fluoropolymer use and the adequacy of ventilation in the work space.[17,19,22,27] In fact, in *post hoc* exposure–response assessment study of 102 affected persons of respiratory illness following inhalation of waterproofing sprays, cases were exposed in a variety of situations, ranging from short to extended spraying and from poorly ventilated rooms to wide open areas.[22]

Clinical syndrome

Illness associated with exposure to fluoropolymer-containing products often resembles polymer fume fever, with acute respiratory signs, and symptoms predominating the clinical picture and often accompanied by flu-like symptoms.[3,4,12] Table 1 summarizes the typical signs and symptoms associated with fluoropolymer use. The commonest symptoms include non-productive cough and dyspnea, affecting 60% or more of patients in one study.[6,8] The illness develops rapidly, usually within minutes to hours. In several studies, over half of the affected patients presented within 1 h.[6,7] Although the persons primarily affected are those using the implicated products, clinical effects have been seen from second-hand exposure in persons who are not directly using product.

Abnormal laboratory studies have generally revealed inflammatory reactions, as evidenced by leukocytosis and elevated CRP.[1–2,4,6,21,25,28] In one case, marked hypocalcemia occurred and was attributed to documented elevations in fluoride concentrations that persisted 30 h after exposure.[1]

Table 1. Symptoms and signs seen in fluoropolymer-associated respiratory illness.

General	Respiratory
• Fever	• Cough (productive)
• Chills	• Shortness of breath
• Malaise	• Tachypnea
• Myalgias	• Wheeze, rales, and rhonci
• Generalized weakness	• Decreased breath sounds
	• Increased work of breathing
Neurologic	Abdominal
• Headache	• Nausea and vomiting
• Dizziness	
Cardiovascular	Skin
• Chest pain/chest tightness	• Pallor
• Tachycardia	

Because fluoride is the most electronegative element, it will bind tightly to cations, such as calcium, causing hypocalcemia similar to that seen following systemic hydrofluoric acid poisoning.[1–2] This patient did not suffer from dysrhythmias.

Most patients recover within 24 h, although recovery has taken days to weeks.[1,3–5,7,16,28] In one study, over 50% of patients required hospital admission.[6] Pulmonary symptoms may last longer than other symptoms, such as nausea and fever.[7,36] Cases requiring endotracheal intubation have been reported.[1,6–8] Complications have included ARDS and two deaths.[1,5,9] While most patients recover fully, persistent symptoms are reported, including lung function abnormalities and pulmonary fibrosis.[12]

Human cases

Numerous outbreaks involving humans have been described involving various products such as leather conditioner, water and soil repellant, floor stain repellant, grout sealant and ski wax.[1,3–4,6,12,23,27–28] Reports describing illness associated with aerosol and non-aerosol products exist; however, cases involving aerosol formulations predominate. These outbreaks have occurred sporadically over several decades with products from various unrelated manufacturers in Asia, Europe and North America. A number of outbreaks have included hundreds of patients, involving widespread product recalls.

One example of an outbreak occurred in Switzerland in 2002 over a two-month period following a formulation change of a floor stain protector.[12] Reportedly, a tiling company had been using the same registered trademark floor stain protector for 4 years without respiratory symptoms until three previously healthy workers became ill with dyspnea and cough. All three patients sought medical care and two patients had hypoxemia and required hospital admission. Investigation of the product revealed a recent formulation change involving the solvent and the water-repelling agent. The following winter, over 150 cases of similar respiratory outbreaks associated with exposure to waterproofing agents were reported. The same fluoropolymer produced by the same manufacturer was found to be the common constituent in all cases.

An unusual episode of respiratory symptoms occurred in a 60-year-old male smoker following intense exposure to ski

waxing vapors.[1] The ski wax, containing a fluoropolymer resin, is melted with a hot iron (200–220°C) and applied to the sole of the ski to improve gliding on the snow. The affected patient fell ill after performing ski maintenance for an entire group of skiers on two consecutive evenings, developing symptoms on the first night, but proceeding to wax 40 pairs of skis on the second night. At the end of the second night, the patient was transported to the hospital, where he was noted to have dyspnea, cough and hypoxemia and ultimately required endotracheal intubation. The patient was extubated on hospital day 3 and was discharged home without residual symptoms on the eighth day. Although the patient was at high altitude (2500 m above sea level) during the ski wax exposure, the authors felt that fluoropolymer pyrolysis, and not high-altitude pulmonary edema (HAPE), was the etiology of the symptoms because he never had dyspnea during his multiple previous trips to even higher altitudes, he had already been at altitude for 12 days prior to developing these symptoms, laboratory and radiographic studies showed inflammation and injury not consistent with HAPE and because his symptoms worsened with standard HAPE treatments (return to low altitude and positive pressure ventilation).

Epidemiology

USA national data on human exposures to aerosol waterproofing agents are reported to the National Poison Data System (NPDS), formerly called the toxic exposure surveillance system (TESS). Data regarding recent exposures have been summarized by previous authors.[8] Although the inhalation route is the route implicated in the respiratory illness outbreaks, it appears as though all routes of exposures increased over time between 2001 and 2006.[8] During this time frame, reported exposures varied with the seasons and were more common in fall and winter months.[3,8,12]

Although many of the case reports describe adult patients, the median age following review of the TESS national database suggested that the median age of exposure was 13 years (mean 18.2 years) in one report and 33 years in another.[3,8] The severity of patient outcomes was associated with increasing age.[8] One abstract describing 91 persons affected from a single German outbreak were predominantly female (77%); however, other reports suggest that those affected are primarily male.[6–8] With regard to the gender predilections described in some reports, this appears related to the implicated product; the reports suggesting a male predilection involve products used in jobs with a stereotypically male predominance, such as grout sealer, whereas the study reporting female predominance involved household products for indoor use sold at local supermarkets.

Most exposures occur following home use of aerosolized products; however occupational exposures are reported.[3,6,8,22,35] Occupational exposures have included persons sealing grout, maintaining skis by applying waterproofing wax. One case of respiratory illness resulting from huffing of the fluoropolymer product is reported.[34] Illness has been reported following product use indoor in areas of poor ventilation; however cases following use outdoors in well-ventilated areas have occurred.[3] Additionally, persons not primarily applying the product have been affected after second-hand exposure, although less frequently than individuals reported to have been using the product themselves.[3] Cases involving indirect exposures have occurred, with symptoms occurring after indoor exposure to evaporating fluoropolymer resin from shoes and boots that were sprayed outside.

Many of these outbreaks occur following a product formulation change,[5,11–12,17,21–22,27] although one case not following a formulation change is reported.[28]

Similarity to other well-described disease entities

Outbreaks of illness associated with fluoropolymer products have appeared similar to polymer fume fever, acute chemical pneumonitis, and reactive airway dysfunction syndrome, occasionally accompanied by nonspecific systemic symptoms, such as fever, chills, malaise, arthralgias, and nausea.[4–5,25,27,37,47–48]

Polymer fume fever differs somewhat from pneumonitis associated with fluoropolymer waterproofing agents. Polymer fume fever is associated with different polymers, usually involves heating or burning the polymer, and more often includes systemic symptoms.

Chemical pneumonitis results from aspiration or inhalation of irritants and has been reported after exposure to various compounds, including hydrocarbon solvents.[1,27,38] This entity usually results from either direct injury to distal airway cells or an exaggeration of normal physiological responses.[4,38] Pathological changes in the distal airways compromise the alveolar capillary interface, potentially leading to pulmonary edema and impaired gas exchange.[38] Chemical pneumonitis can result in permanent effects such as reactive airway dysfunction syndrome (RADS) and bronchiolitis obliterans, a clinical picture similar to that seen after some waterproofing agent exposures.[49,50] Treatment is usually supportive.[27]

Reactive airways dysfunction syndrome (RADS) involves bronchial hyper-reactivity resulting from respiratory exposure to irritant gas smoke, fume, or vapor and has been associated with exposure to a fluoropolymer.[27,39] Symptoms mimic that of asthma and include shortness of breath, cough, chest tightness, and wheeze. Diagnostic criteria for RADS include symptom onset within 24 h of exposure, persistence for at least three months, nonspecific bronchial hyper-responsiveness, airflow obstruction demonstrated by pulmonary function test, and exclusion of other causes.[39–42] Chemicals that are most frequently associated with RADS include chlorine, toluene, diisocyanate and oxides of nitrogen.[27] Treatment of RADS is supportive, involves serial monitoring of patient symptoms and lung function and may include steroids, beta-2 adrenergic agonists and anticholinergics.

Other diseases with similar symptoms include atypical pneumonia, congestive heart failure, and hypersensitivity pneumonitis.[4]

Management of symptomatic fluoropolymer exposures

Treatment with basic and supportive measures, including fresh air and supplemental oxygen, are sufficient in many

cases.[1–4,6,8,12,27–28] Inhaled beta-2 adrenergic agonists and corticosteroids have been used in some cases.[3,4,12,27–28,34] Based on physical exam evidence of bronchospasm in these patients, the reported improvements with these measures, the relative safety of these medications, we feel that treatment with inhaled beta-2 adrenergic agonists and corticosteroids is reasonable. Non-invasive positive pressure ventilation and endotracheal intubation have been required in some cases.[1] Some patients have received antibiotics as pneumonia was included in the differential diagnosis.[8] We feel that treatment with antibiotics should be reserved for patients with clinical findings consistent with respiratory infection.

Poison centers in the US and Europe have played a crucial role in the recognition of these disease outbreaks, with voluntary recalls beginning the first few days after the first reported illness in many cases.[4,5,17]

Prevention of excessive exposure

Consumers should be certain that all commercially available waterproofing agents are used only as directed and be mindful that ease of access to these products does not imply that they are nontoxic.[3] Education aimed at increasing awareness and understanding of this problem might help avoid future breakouts, and seasonal trends suggest that this education should be focused on fall and winter months.[8] General sanitation procedures, such as use of dermal protection if skin contact is likely; use in well-ventilated areas (outdoors if possible); frequent hand washing, especially before eating; and avoidance of smoking to avoid exposure to pyrolysis products, should be encouraged.[12,22–23,43]

Workplace education may decrease occupational illnesses associated with fluoropolymer-containing products.[12] In addition to those measures taken by the average consumer, employers might install and maintain local exhaust in proximity to areas where fluoropolymers are commonly used.[43] Workers should apply product by paintbrush when possible.[12,23]

Many of these products do not note the presence of a fluoropolymer on the MSDS as it often comprises less than 1% of the total ingredients.[6] In addition, identifying the primary manufacturer of some of these products is difficult as several levels of distributors may be involved in the packaging and marketing of the final product, further complicating efforts to obtain the MSDS.[6] Additionally, if identified, the manufacturer is sometimes reluctant to release specific information regarding active ingredients, as these are sometimes considered "proprietary in nature."[6] Clearly listing the primary manufacturer and the presence of fluoropolymers on product containers, perhaps with an obvious warning label, might alleviate some of these issues.[12,43]

Conclusion

Fluoropolymer aerosol waterproofing agents can produce abrupt onset of symptoms, which principally include dyspnea and cough. Most victims improve with supportive care and supplemental oxygen. However, beta-2 adrenergic agonists and corticosteroids may be helpful in some cases. Serious outcomes have been reported, including ARDS, the need for endotracheal intubation and death, but are uncommon. Better education is needed to increase awareness and to prevent future exposures. Further research should focus on the mechanism of action, safe exposure limits, and optimal treatment of moderate and severe cases.

Declaration of interest

The authors report no declarations of interest. The authors alone are responsible for the content and writing of the paper.

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Supplementary material available online

Supplementary Table 1.