

Occupational lung disease · 5

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Respiratory irritants encountered at work

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Respiratory irritants cause acute lung injury. Their effects are distinguished from hypersensitivity induced lung injury by their mechanism of action – a direct toxic effect – and the speed of onset – within minutes or hours rather than months or years. Respiratory irritants may be inhaled or transported to the lungs by the circulation. This article focuses on the long term consequences of inhaled respiratory irritants on the airways.

Inhaled respiratory irritants provoke an acute inflammatory response with injury to the epithelial cells of the lungs. Depending on the site of uptake or deposition of the irritant, these effects predominantly involve the upper respiratory tract and airways or the gas exchanging parts of the lungs (fig 1). Irritants may be inhaled as gases or vapours, solid particles, or liquid aerosols. In general, water soluble gases and vapours and particles of aerodynamic diameter greater than $5\ \mu\text{m}$ are deposited in the upper respiratory tract and proximal airways. Water insoluble gases, vapours and fumes, and particles whose aerodynamic diameter is $0.5\text{--}5\ \mu\text{m}$ can penetrate into and be deposited or taken up in peripheral airways and the gas exchanging parts of the lung. Irritants deposited or dissolved in the upper respiratory tract and proximal airways may cause injury to airway mucosal cells, exaggerated physiological responses, an acute inflammatory reaction, or all three of these. Exaggerated physiological responses include cough (from stimulation of

afferent nerve endings in the airway mucosa), mucus secretion (by submucosal and goblet cells), and acute airway narrowing which, in the case of inhaled sulphur dioxide, occurs at concentrations considerably below those causing mucosal cell injury. Irritants deposited in the gas exchanging parts of the lungs cause injury predominantly to endothelial and type I epithelial cells, and pulmonary oedema with plasma exudation into the air spaces. Water soluble agents such as sulphur dioxide and ammonia provoke irritation and inflammation of the moist mucosal surfaces of the eyes, nose, throat, larynx, and proximal airways within seconds (or, at most, minutes), alerting those exposed to the irritant. Water insoluble agents such as oxides of nitrogen and fumes of cadmium or beryllium do not provoke an immediate irritant reaction and those exposed are unaware of the irritant and may therefore remain exposed for considerable periods, accumulating high doses. The severity and pattern of the response are influenced by the inhaled dose. The effects of chlorine, a gas of intermediate water solubility, are limited to the upper respiratory tract and proximal airways when inhaled in low concentrations, but when inhaled in high concentrations it causes pulmonary oedema. Similarly, although ammonia and sulphur dioxide are very water soluble, those exposed to it in enclosed spaces from which they are unable to escape may die of pulmonary oedema.

Although the immediate effects of the individual respiratory irritants have been well characterised, the effects of complex mixtures such as smoke, whose components may vary in nature and concentration according to circumstances, and the long term effects of inhalation of respiratory irritants are less clear. This has been mainly due to a lack of information about individual lung function before the inhalation and therefore lung function after the event has to be compared with what would be expected for that individual from values obtained for the general population, a far from satisfactory basis for comparison. Nonetheless, chronic airway diseases have been reported to follow inhalation of short duration of respiratory irritants in toxic concentrations. These include chronic airways limitation and asthma.

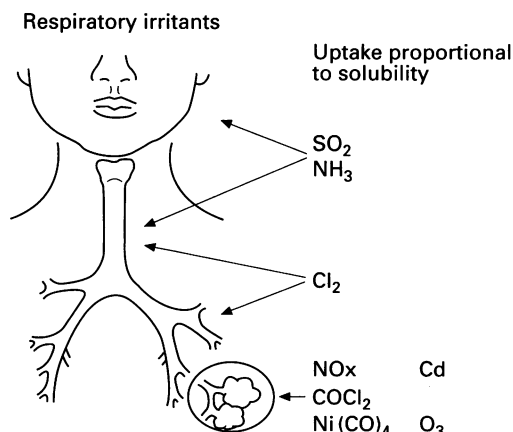


Figure 1 Predominant site of damage to the lungs caused by respiratory irritants.

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Table 1 Distribution and rates of inhalation accidents by occupation, 1990–3

Occupational group*	Estimated cases	Rate/million/year
Chemical processors	156	163.5
Engineers/electricians	343	32.1
Other manufacturers	163	14.8
Transport/construction	100	9.8
Health and scientific professionals	59	9.0
Sales and services	163	6.1
Others	121	3.1
Total	1061	10.6

* Occupational classification by job title, OPCS classification with modifications. Population data from the 1991 Census Report for Great Britain.

Table 2 Suspected agents in inhalation accidents 1990–3

Agents	Accidents
Gases	36%
Organic chemicals	22%
Inorganic chemicals	14%
Combustion products	10%
Metals	5%
Miscellaneous	6%
Not specified	0.4%
Total no.	869

Estimated incidence of acute inhalation accidents in the UK (SWORD)

Reliable information on the frequency of acute inhalation accidents at work and their causes and consequences is scarce worldwide. In the UK the Surveillance of Work and Occupational Respiratory Disease (SWORD), to which the majority of chest physicians and a large number of occupational physicians have, since 1989, reported *new* cases of occupational lung disease which they have seen, provides for the first time a reliable basis for estimating the incidence and outcome of acute inhalation accidents in the UK. In the five year period between 1990 and 1994 an estimated 1180 inhalation accidents were reported, representing about 10% of all occupational lung diseases reported – the fifth most common disease category.¹ The incidence was five times greater in men than in women, with the highest rates among chemical processors followed by engineers and electricians (table 1). Most of the cases were caused by inhaled chemicals (table 2), of which chlorine was the most frequently reported agent (12% of cases) with oxides of nitrogen in 9% of cases. Surprisingly, the incidence rate in young men was less than in men aged between 30 and 60 years (fig 2).¹

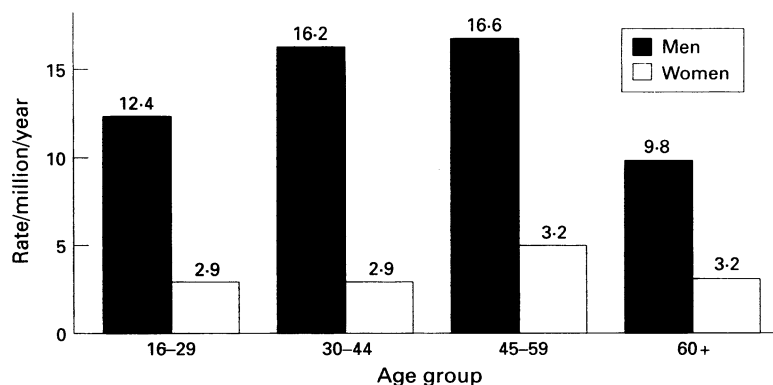


Figure 2 Inhalation accident rates by age and sex, 1990–3. Rates are higher in men at all ages and highest in men in age groups 30–44 and 45–59.

Long term consequences of acute inhalation accidents

CHRONIC AIRFLOW LIMITATION

The outcome of acute lung injury caused by inhaled respiratory irritants has been disputed since the aftermath of the use of chemicals such as chlorine, phosgene, and sulphur mustard as weapons of war in the 1914–18 war. The problem then, as now, has been to make an unbiased estimate of what would have occurred in the absence of exposure as a basis for comparison with what was observed. The survivors of the 1914–18 war suffered the consequences of several potential adverse influences on the function of their lungs, including a high rate of respiratory infections in infancy and early childhood, the influenza pandemic of 1919, and the epidemic of cigarette smoking initiated during the early years of the century. More recently reported studies face the same issues of comparing “like with like”. In the absence of knowledge of respiratory symptoms and function before an inhalation accident, findings in exposed individuals are compared with “predicted values” in a “normal population”, a basis for comparison likely to be particularly insecure for cases who have been seen and followed up in hospital. Despite these limitations, a number of studies have been reported which provide some guidance with regard to the long term consequences of inhalation accidents.

A cross sectional survey of pulp mill workers in British Columbia found that more than half of the workforce (189 of 321) reported involvement in one or more chlorine “gassing” incidents in the past.² They were more likely to report wheezing than other pulp mill workers or a comparison group of railway yard workers. In addition, when compared with other pulp mill workers, non-smokers who reported “gassing” episodes had a lower ratio of forced expiratory volume in one second (FEV₁) to forced vital capacity (FVC) and lower flow rates at low lung volumes. However, a major difficulty in interpreting these observations, as the authors of the study recognised, is the potential for bias in recall of “gassing” accidents by those with respiratory symptoms and reduced lung function.

Schwartz *et al* followed up a group of 20 construction workers for up to 12 years after an accidental exposure to chlorine at a pulp mill.³ Lung function tests on the day following the inhalation accident showed a reduced FEV₁/FVC ratio (<65%) in 40% of those exposed and an increase in residual volume (RV) in 60%. The increased RV had resolved by one year but the high prevalence of a reduced FEV₁/FVC ratio persisted during the 12 year follow up period. However, the mean loss of FEV₁ during this period was no greater than 25 ml/year. The authors interpreted this as suggesting that the accidental chlorine inhalation was not responsible for the persistent airflow limitation and attributed the high proportion of cases with a reduced FEV₁/FVC ratio to the high prevalence of smokers in their study group. However, the increase in RV which reversed during the first year of follow up was probably the consequence of the chlorine exposure.

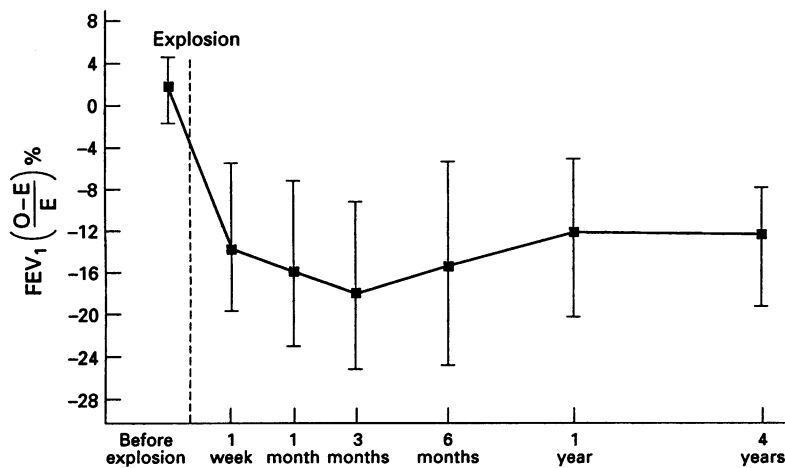


Figure 3 Forced expiratory volume in one second (FEV₁), expressed as the percentage difference from predicted, before and after accidental exposure to sulphur dioxide (after ref 5).

Jones *et al* studied the survivors of an accident in which chlorine leaked from a derailed train causing the deaths of eight persons, 23 hospital admissions, and evidence of respiratory injury in a further 25.⁴ The 60 adults followed up during the subsequent six year period included 20 of the 23 hospital admissions and 21 of the 25 with respiratory injury. They showed an average annual fall in FEV₁ of 18 ml/year in non-smokers and 34 ml/year in current smokers. Neither the distance from the chlorine source nor the severity of the initial response to chlorine inhalation had a discernible effect on the rate of decline of lung function. However, as lung function had not been measured before exposure to the chlorine, the authors were unable to exclude a permanent reduction in lung function not reflected in its subsequent rate of decline.

One of the few studies that has been able to overcome this problem was a survey of the outcome in seven miners of inhalation for 20–45 minutes of toxic concentrations of sulphur dioxide generated in a pyrite dust explosion.⁵ One man died from pulmonary oedema. The survivors had all undergone regular lung function testing during employment before the accident, and this was continued during the following four years. The maximum reduction in FEV₁ and FVC occurred one week after the accident; the mean FEV₁ was 18% less than predicted compared with values of better than predicted before the accident (fig 3). The improvement after one week plateaued after four weeks at levels well below the pre-accident values, with the FEV₁ on a mean 13% less than predicted. No further improvement occurred during the follow up period of four years. Four of the seven survivors also had increased airways responsiveness to inhaled histamine at four years. Gas transfer coefficient (Kco) was normal in all seven.

Several studies have reported the outcome in individuals who have survived acute severe smoke inhalation. Kinsella *et al* measured lung function in 13 consecutive patients treated at Glasgow Royal Infirmary for smoke inhalation three weeks and three months after an inhalation accident.⁶ Initial specific airway

conductance was correlated with carboxyhaemoglobin concentration, a measure of inhaled smoke dose. The initial mean concentration of histamine causing a 20% fall in FEV₁ (PC₂₀) was 1.65 mg/ml; only one of the 13 had an initial PC₂₀ of more than 8 mg/ml. Three months later the median histamine PC₂₀ was 5.43 mg/ml with improvement in 10, no change in one, and falls in two. The FEV₁ was, on average, 76% of the mean predicted value initially and showed no improvement at three months. Fogarty *et al* studied 14 survivors from the underground fire at King's Cross, London in November 1987 which killed 31 and is known to have injured a further 27 people, one of whom died in hospital.⁷ The 14 survivors in the study group had inhaled substantial quantities of smoke; 10 had suffered skin burns. Mean values for FEV₁ and FVC, TLC₀, and Kco were within 95% confidence intervals of the predicted values in both smokers and non-smokers. At six months and two years the mean residual volume was at the upper and mean V₂₅ at the lower 95% confidence limits, suggesting a persistent abnormality in the small airways.

O'Hickey *et al* followed up the 15 survivors admitted to hospital from the Manchester air disaster in which an aeroplane caught fire on the ground in August 1985 causing the deaths of 52 of the 137 passengers and crew on board.⁸ Eight of the 13 were treated in the intensive care unit, one with adult respiratory distress syndrome (ARDS). Four were ventilated. All eight had significantly reduced FEV₁ and FVC but gas transfer, measured after assisted ventilation was discontinued, was normal. In the less severely affected group lung function tests were measured within 24 hours of admission. FEV₁ and FVC improved during the week after the accident, particularly in one asthmatic patient. At follow up some three months later the respiratory symptoms had resolved in the less severely affected group, but wheezing and shortness of breath persisted in the eight severely affected subjects. Lung function had returned to normal in most, but airway responsiveness was markedly increased in two asthmatic patients who required more treatment than before the accident and was mildly increased in a further three.

IRRITANT INDUCED ASTHMA

Irritant induced occupational asthma (reactive airways dysfunction syndrome (RADS)) is persistent asthma and airway hyperresponsiveness which develops after acute inhalation of a respiratory irritant in toxic concentrations. The onset of respiratory symptoms and the presence of airway hyperresponsiveness within a few hours of exposure to an identifiable irritant distinguishes irritant induced asthma from hypersensitivity induced occupational asthma. The criteria used to identify irritant induced asthma are shown in table 3.

Most descriptions of irritant induced asthma have been reported in case series. The original report described 10 patients, none of whom had evidence of pre-existing respiratory disease.⁹ All developed persistent asthma after a single

Table 3 Criteria for the diagnosis of irritant induced asthma (reactive airways dysfunction syndrome)

1. Absence of preceding respiratory complaints.
2. Onset of symptoms occurring after a single specific exposure incident or accident.
3. Exposure was to a gas, smoke, fume or vapour that was present in very high concentrations and had irritant qualities.
4. Onset of symptoms occurring within 24 hours after the exposure and persisting for at least three months.
5. Symptoms consistent with asthma, with cough, wheezing and dyspnoea predominating.
6. Pulmonary function tests may show airflow obstruction.
7. Appropriate challenge testing showing increasing airway responsiveness.
8. Other types of pulmonary diseases excluded.

exposure – usually of only a few minutes duration although in one it lasted 12 hours – to a variety of respiratory irritants. These included a spray paint containing ammonia, heated acid, floor sealant, uranium hexafluoride, and smoke. The onset of respiratory symptoms was immediate in three with an average interval of nine hours in the others. The duration of symptoms to the time of follow up ranged from one to 12 years, by which time static lung function tests were normal in three, but the remaining seven had evidence of airflow limitation; all 10 had increased airway responsiveness to inhaled methacholine. Subsequent reports of irritant induced asthma have documented asthma induced by a single inhalation in a toxic concentration of a variety of agents including sulphur dioxide,⁵ toluene diisocyanate,¹⁰ anhydrous ammonia fumes,¹¹ and smoke.¹²

Case reports and case series such as these suggest that acute inhalation of an irritant chemical in toxic concentration can initiate symptomatic asthma and increase airway responsiveness. However, the cases reported are highly selected and are without objective measures of lung function made before the inhalation accident, thus limiting the strength of causal inferences which can be drawn. However, one study of hospital employees exposed to 100% acetic acid after a spillage in a hospital laboratory in large part overcame these problems by (1) studying a sample of the exposed population, (2) demonstrating an exposure-response relationship between the estimated intensity of the exposure and the prevalence of irritant induced asthma symptoms and measured airway hyperresponsiveness (the risk of developing irritant induced asthma was 10 times higher for those most highly exposed to acetic acid than for those less exposed following the spill), and (3) partial validation of respiratory health prior to the accident by examination of pre-employment health questionnaires.¹³

The incidence of irritant induced asthma is not known but an estimate can be made for England and Wales from SWORD data.¹ Physicians participating in the scheme were asked by questionnaire about the outcome of 623 cases of inhalation accidents reported during a 3.5 year period between January 1990 and July 1993. Of the 383 patients where the occupational physician was aware of the diagnosis, 70% had recovered within one week, 78% of the patients had returned to work within one week, 12% had symptoms for more than one month, and a further 2% did not return

to work. Of the 47 cases with persistent ill health, 11 (23%) developed asthma or irritant induced asthma. The agents associated in these cases were mainly respiratory irritants which included chlorine, oxides of nitrogen, sulphur dioxide, ammonium, carboxylic acid, and sodium fumes.

Few reports have been published of the pathological changes in the airways of patients with irritant induced asthma. Bronchial biopsy specimens in some of the original cases reported by Brooks *et al* showed bronchial epithelial cell injury with desquamation and bronchial wall inflammation, with infiltration of plasma cells and lymphocytes but not eosinophils.⁹ A later study of bronchial biopsy specimens in four men with irritant induced asthma 1–32 months after inhalation of ammonia reported denuded epithelium, submucosal chronic inflammation, and focal thickening of the basement membrane.¹⁴

More recently, Gautrin *et al* reported the changes observed in the bronchial biopsy specimens of five cases of irritant induced asthma following chlorine inhalation 1–2 years previously.¹⁵ All had airway hyperresponsiveness. None were current smokers nor had any received treatment with oral or inhaled steroids since the inhalation accidents. The changes observed were mucosal desquamation with marked subepithelial thickening with fibrosis, but no increase in eosinophils. The authors also found that, on average, these cases had less reversibility to inhaled β agonists than patients with hypersensitivity induced occupational asthma with comparable severity of airflow limitation, which they suggested might be related to the differences in the pathological changes.

Conclusions

The long term consequences of inhaled respiratory irritants have been a source of controversy since the aftermath of gas warfare in World War I. Accidents by their nature occur unexpectedly and generally involve only a few persons. Their effects, both acute and chronic, are at least in part determined by the health of the individual at the time of the accident. The patterns of response of the lungs to injury are limited and the lack of specificity can make it difficult to distinguish the effects of an inhalation accident from other diseases of the lungs common in the community – particularly airflow limitation, both reversible and irreversible. These are not issues which can be readily addressed in case reports and series which form most of the reports of inhalation accidents.

Nonetheless, there is sufficient evidence to make it likely that some inhaled respiratory irritants can cause chronic airways disease. The study of the six pyrites miners who inhaled sulphur dioxide in toxic concentrations, which included measurements of lung function before the explosion, revealed an initial reduction in FEV₁ and FVC with little variability between cases, and a plateau considerably below the values recorded before the accidents.⁵ Similar

changes, but without knowledge of lung function before the inhalation accident, have been suggested by the findings in other studies. Similarly, although most reports of irritant induced asthma have been case series, the study by Kern of hospital staff who had inhaled acetic acid demonstrated a relationship, in a random sample of the exposed population, between the prevalence of asthmatic symptoms and the measured airway hyperresponsiveness and the estimated intensity of exposure to acetic acid.¹³ A systematic exposure/response relationship provides strong evidence of a causal relationship and was supported by the responses to a pre-employment questionnaire.

The nature of the pathological changes in the airways caused by inhaled respiratory irritants has not been extensively documented. Obliteration and organisation within bronchioles has been reported after the inhalation of oxides of nitrogen¹⁶ which is consistent with the pattern of functional abnormalities observed.¹⁷ Chronic asthma following inhalation accidents has been associated with evidence of airway mucosal inflammation and thickening of the basement membrane.

The reports made to SWORD by occupational and chest physicians make it clear that inhalation accidents are a frequent and largely preventable cause of work related ill health – most cases were attributed to spills, leakages, faulty processes, lack of respiratory protection, and failure to observe safety guidelines – which can have substantial long term medical, social, and financial consequences.

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