Case Study

Respiratory Health in Aseptic Packaging with Hydrogen Peroxide: A Report of Two Cases

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In the consumer market, there is an increasing demand for various types of fruit juices. To prevent rapid deterioration of the juice the packaging is performed aseptically, commonly employing 5–35% hydrogen peroxide. The workers who operate the packaging machines may encounter inhalation exposure to hydrogen peroxide vapours, and incidental splashes or skin contact with the substance are also possible.

Hydrogen peroxide (H₂O₂) is an endogenous metabolite of oxygen and occurs at submicromolar concentrations in aerobic cells. Hydrogen peroxide is able to penetrate biological membranes like water, and the substance oxidises biomolecules unless it is degraded to oxygen and water which readily happens in the presence of catalase or glutathione peroxidase1). After oral ingestion or surgical application to body cavities, the rapid breakdown of H₂O₂ may result in oxygen embolism, sometimes with serious consequences²–⁴). In local contact, hydrogen peroxide is irritating or corrosive depending on the concentration. Workers engaged in tank loading complained of nose irritation at a measured vapour concentration of 3.5 mg/m³⁵). In a controlled study with volunteer subjects, the threshold concentration of the airborne vapour for airway irritancy was 10 mg/m³⁶).

In the eye, 5% hydrogen peroxide water solution is irritating, and a concentration of 8% or higher caused irreversible damage in the rabbit eye⁷,⁸). In rabbit skin, a 10% solution in water was mildly irritating and a 35% solution caused epidermal necrosis probably due to oxygen embolism in the capillaries, whereas 50% or higher concentrations were corrosive⁹). Many workers have noted that inadvertent skin contact to the more concentrated solutions causes white spots which spontaneously disappear within some hours; the change of colour is due to formation of oxygen microbubbles in the skin. Based on a review of historical skin testing results involving hairdressers at two dermatological clinics, hydrogen peroxide is not a skin sensitiser¹⁰).

Long term effects of hydrogen peroxide vapours in the respiratory system have not been adequately elucidated. A limited study performed fifty years ago with dogs suggested that hydrogen peroxide induced lung toxicity at 10 mg/m³¹¹). In the open literature, there is a case report of a heavily exposed dairy worker who developed interstitial pneumonitis, which the authors attributed to hydrogen peroxide exposure¹²).

Presently, the lack of reliable data precludes any possibility of making a health risk assessment for workers who are typically exposed to hydrogen peroxide via inhalation. It would therefore be worthwhile to gather such information from occupational health monitoring programmes and, after critical data analysis, to report them. The present paper deals with the symptoms and respiratory morbidity experienced by a small group of workers exposed to hydrogen peroxide at a fruit juice factory. Although this investigation is limited by the small number of persons involved, and the restricted method employed, the special circumstances of a change in exposure from high to reasonably low levels, and monitoring of the health status over time, add more weight to the study.

Methods

Circumstances of the study

The occupational health personnel and the researchers were alerted in the summer of 1999 by complaints of eye and airway irritation among workers operating two aseptic packaging machines situated side by side in one end of a large hall of a fruit juice factory. The hall also contained four other packaging machines which caused minimal exposure but were not associated with any complaints. After the discovery of high airborne hydrogen peroxide vapour levels, and intermittent skin contact with the substance following the opening of enclosures and manual corrective actions at times of machine failure, technical measures were taken to improve conditions, and the workers’ health status and exposure were closely monitored. Nevertheless, although improvements were gradually made, the targeted low exposure levels were not reached earlier than the spring of 2000. In the spring of 2000, it was decided to conduct a health and exposure study, and the study purpose was explained to all workers in the plant. Workers who gave informed consent were
enrolled in the study. The conduct of the study complied with the principles of the Declaration of Helsinki by the World Medical Association (last revised in the 52nd General Assembly, Edinburgh, Scotland, October 2000).

**Exposure conditions**

The fruit juice production had gradually started in the spring of 1998, hence all the packaging workers had exposure to hydrogen peroxide for 3 yr or less. At the plant the juices were packed in cartons coated with polyethylene. In a typical machine, the laminated paper passed through a bath of 35% hydrogen peroxide water solution after which rollers removed most of the peroxide and sterile hot air at 100°C blows away the remainder. Then the carton is formed and filled with juice. There is overpressure inside the machine. During the disinfection, some H₂O₂ breaks down but most of it evaporates, and the surrounding local exhausts prevent the dispersion of substances into workroom air.

Airborne levels of hydrogen peroxide around the machines were estimated with Dräger indicator tubes (Dräger Tube 8101041, Hydrogen Peroxide 0.1a; Dräger Sicherheitstechnik GmbH, Lübeck, Germany) repeatedly during the shift and during sterilisation at the beginning of the morning shift. Time-weighted average concentrations (mg/m³) for 8 h were calculated based on the levels found with the direct reading instrument at each stage of the shift, and the duration of the stages. According to the supplier, at the low concentration range of 0.1–3 ppm, the variation in repeated measurements (coefficient of variation) is ±10–15% and, correspondingly, ±35% at high levels up to 20 ppm. The detection limit is about 0.14 mg/m³. Two machines caused high exposure, and the remaining machines low exposure (Table 1). This situation prevailed from the summer of 1999 until the spring of 2000; but during the subsequent year, after many technical improvements, reasonably low levels were found at all machines. In other parts of the plant, the air was not found to contain detectable amounts of hydrogen peroxide.

**Health monitoring**

All 6 workers assigned to the heavily exposing packaging machines were enrolled in the health study which included a symptom questionnaire dealing with eye, nasal and throat symptoms, cough and phlegm, asthmatic and skin symptoms, and assessment of the clinical history of respiratory illnesses retrospectively (autumn 1998–spring 2000) and prospectively (spring 2000–spring 2001) based on the records of the company occupational health care unit and sick leave documents written by other doctors. Additionally, 4 workers from other packaging machines, and 10 workers from other departments (with no exposure to hydrogen peroxide) were enrolled in the study, but since only about half of the personnel in those groups volunteered, formal comparisons among the groups were deemed inappropriate due to possible selection processes.

**Results**

**Symptoms and signs**

In the symptom query, every other person in the heavily exposed group reported on irritation: redness and burning in the eyes, blocked nose, itching and dryness in the throat, cough induced by work assignments, and asthma symptoms. Most symptoms became worse at work, and were aggravated towards the end of the workweek.

In the context of walk-through surveys in the aseptic packaging hall during 1999, the occupational health team had documented reports of adverse effects which occurred when workers intermittently opened enclosures to amend breakdowns of a machine. The symptoms peaked during the period from September 1999 to February 2000. A strong feeling of irritation in the throat and chest, drying and crusting of the nasal mucosa, and blocked nose were noted. Many workers also reported on burning in the eyes, headache, protracted dry cough and temporary loss of olfaction. Workers who handled cartons inside the machine during disruptions even reported skin effects: burning and pricking of the fingers, drying of the hands and face, decrease in skin elasticity and change in colour. The hair was blanched and felt dry and rough.

**Respiratory morbidity**

According to the plant physician’s records two machine operators and one maintenance worker exhibited a uniform course of recurring bronchitis-sinusitis which included a symptom questionnaire dealing with eye, nasal and throat symptoms, cough and phlegm, asthmatic and skin symptoms, and assessment of the clinical history of respiratory illnesses retrospectively (autumn 1998–spring 2000) and prospectively (spring 2000–spring 2001) based on the records of the company occupational health care unit and sick leave documents written by other doctors. Additionally, 4 workers from other packaging machines, and 10 workers from other departments (with no exposure to hydrogen peroxide) were enrolled in the study, but since only about half of the personnel in those groups volunteered, formal comparisons among the groups were deemed inappropriate due to possible selection processes.

**Table 1.** Exposure (8h TWA, mg/m³) to hydrogen peroxide in aseptic packaging.

<table>
<thead>
<tr>
<th>Location</th>
<th>Concentration before improvements</th>
<th>Concentration after improvements</th>
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<tbody>
<tr>
<td>Two machines at one end of the hall</td>
<td>1.7–3.4*</td>
<td>0.5–0.7</td>
</tr>
<tr>
<td>Other machines</td>
<td>0.2–0.6</td>
<td>0.2–0.6</td>
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*At one machine the highest levels were 11.3 mg/m³ (8 ppm) during morning sterilisation (lasting 1.5 h). When the machine was in operation (6 h) transient peak levels, repeated several times per hour, were 8.5 mg/m³ (6 ppm). At another machine the highest peaks were 4.2 mg/m³ (3 ppm).
started in the early autumn of 1999 and continued until the spring of 2000. Typical symptoms were smarting pain in the nose and throat, blocked nose and pain in the region of the nasal sinuses, headache after the workday, smarting pain and redness in the eyes, and bronchitis with a dry cough. In one patient the history of respiratory infections started acutely with pneumonia. Although the infections in general responded favourably to the administration of antibiotics, the dry cough and headache persisted, and two patients (for more details, see below) made a full recovery only after administration of inhaled corticosteroids and a concurrent reduction in airborne hydrogen peroxide levels.

**Patient 1**

The patient was a 55-yr-old nonsmoking woman who had operated an aseptic packaging machine since March 1998.

Earlier illnesses: About 20 yr earlier the patient was examined with oesophagoscopy and bronchoscopy because of laryngeal symptoms. A biopsy sample from the tracheal bifurcation indicated chronic inflammation but the patient did not exhibit chronic bronchitis. Strumectomy was performed in 1988, and thyroxin substitution was found necessary after the operation. Skin prick testing suggested hay allergy, but the patient did not have atopic symptoms.

**Present illness:**

September 1999: On returning to work from a summer holiday the patient developed airway irritation symptoms and subsequently flu which was complicated by bilateral maxillary sinusitis. The infection was treated with doxicyclin for 10 d.

October 1999: One and a half months after the previous illness, on returning to work from a week’s holiday, the patient experienced blocked nose, headache, pain in the maxillary region and chest tightness. The skin of the hands was found to be blanched, thickened and inelastic. In pulmonary auscultation, bronchial sounds were heard. Peak expiratory flow (PEF) measured with a Wright peak flow meter (Airmed, Clement Clarke International Ltd, Harlow, Essex, UK) was 460 l/min (reference value 470 l/min). The peak flow measurement was done according to the recommendations of Quanjer et al. and the Gregg and Nunn reference values. Chest X-ray: a slight residual consistent with past infection, a radiograph of the nasal sinuses: a mild ethmoidomaxillary sinusitis. Five days later the patient said that after morning sterilisation (with peak exposure to peroxide) she developed dyspnea, smarting in the upper airways, headache, and loss of olfaction. Lung auscultation revealed bronchial sounds with a wheeze. PEF was 420 l/min. The patient was given budesonide inhalation aerosol 200 μg twice daily, inhaled salbutamol as needed, and doxicyclin for the sinusitis.

November 1999: After a 5-d sick leave the patient returned to work and reported chest tightness. In a physical examination, signs of airway obstruction were found, PEF was 420 l/min. Four weeks later, after three weeks at work, the patient experienced increasing cough, dyspnea, phlegm and a slightly high temperature. Pulmonary auscultation indicated obstruction and moist rales. The PEF was 390 l/min. The asthma medication was supplemented with roxitromycin 150 mg twice daily because of the febrile bronchitis.

December 1999: On Christmas Day the patient had acute symptoms consistent with Influenza A/Sydney virus infection. The febrile illness was complicated by prolonged bronchitis which was treated with cephalochlor 500 mg three times daily.

February 2000: The patient was for two weeks on a holiday trip in the Caribbean and was symptomless without inhaled salbutamol.

March 2000: Nasal symptoms and wheezing were again aggravated. Bronchial sounds were noted in lung auscultation and inhaled steroids were stopped in view of the forthcoming lung function studies.

April–May 2000: Exposure to peroxide at work was greatly reduced. Nasal symptoms and dyspnea were also relieved. Examinations at a pulmonary outpatient department showed mild bronchial hyperreactivity in the histamine challenge test. The test was performed according to Sovijärvi’s method which follows FEV₁ (forced expiratory volume in one second) values with a Vitalograph S bellow spirometer (Vitalograph, Buckingham, England). A 15% reduction in FEV₁ was considered significant, and the provocative dose of histamine diphosphate causing a 15% reduction in FEV₁ (PD₁₅) was measured. The patient’s result was 1.3 mg (hyperresponsiveness is graded as slight at 0.41–1.6 mg). Spirometry was normal. PEF levels without medication ranged 360–430 l/min and the corresponding values during a short-lasting sympathomimetic were 410–470 l/min (no significant bronchodilation response). Skin prick tests gave a positive reaction only to dog epithelium.

**Patient 2**

The patient was a 34-yr-old packaging machine maintenance worker (since September 1998) who had smoked one pack of cigarettes per day for 15 y.

Earlier illnesses: In the context of a nosebleed some 15 yr ago the patient was found to have von Willebrand’s disease with no further clinical consequences. His general health status was good. He had no atopy or allergic diseases and had no known predisposition to e.g. asthma in the family.

**Present illness:**

August 1999: On the last day of a workweek the patient
extended his working hours to complete the maintenance of a packaging machine and while working felt a pricking smell which caused attacks of dry coughing. The coughing continued at home and his temperature rose to 40°C. In laboratory examinations two days later the sedimentation rate was 20 and the C-reactive protein 100, and the chest radiograph showed a pneumonic infiltrate in the middle field of the right lung. The patient had a rapid recovery from the pneumonia after receiving doxicyclin (150 mg once daily) for two weeks, and the thorax X-ray was normal after a month.

October–November 1999: After recovery from the pneumonia the patient’s cough continued especially at work where hydrogen peroxide vapour inside the packaging machine caused smarting pain in the upper airways and sore throat. There was a nonproductive dry cough and some tightness in the chest. Despite the continuing symptoms the patient waited until late November before contacting his doctor who in auscultation found bronchial breathing sounds. The PEF measurement was 630 l/min (reference value 630 l/min).

December 1999–March 2000: The patient contacted his doctor towards the end of March and said that he had suffered from a cough as well as burning and redness in the eyes throughout the winter. Lung sounds were bronchial with occasional wheezes on expiration. The conjunctivae of both eyes were swollen. Clinical chemistry and haematology results, and the chest radiograph were normal. PEF was 580 l/min. The patient was administered budesonide inhalation aerosol 400 µg twice daily and dexamethasone-chloramphenicol eye drops.

April 2000: On returning from a week’s sick leave the patient still had some cough but the tightness in the chest and wheezing were relieved. Lung sounds were bronchial and there were some moist rales. Redness in the eyes was much decreased. PEF was 600 l/min. Budesonide dosing was halved to 200 µg twice daily.

May 2000: The patient’s clinical status was much improved although there was still occasional coughing and smart in the eyes. Lung auscultation was normal. The conjunctivae showed slight oedema and hyperaemia under the magnifying glass. PEF was 620 l/min. Treatment with budesonide was continued for another month.

June 2000: The patient was seen because of a mechanical trauma. Respiratory and eye symptoms and signs were gone.

Discussion

Our observations, in keeping with earlier data5–6, indicate that 8-h TWA exposure to about 2–3 mg/m³ of hydrogen peroxide vapour with intermittent peaks at 4–11 mg/m³ causes irritation in the upper and lower airways. Other symptoms caused by the intensive exposure were headache, temporary loss of olfaction, blanching of the hair, and the hair becoming dry and rough. Apart from the well known white spots in the skin after contact with peroxide solutions, the workers reported pricking of the skin of the face and hands, and drying, thickening and inelasticity of the hand skin after manual handling during machine breakdowns. Kondrashov6 concluded from experiments with rats that repeated exposure to peroxide vapours causes effects in the skin at lower levels (1 mg/m³) than in the respiratory system.

Regarding the effects of high concentrations on rats, about 400 mg/m³ hydrogen peroxide vapour in air for 4–8 h caused congestion in the trachea and lungs, and localized areas of alveolar oedema and emphysema, but not mortality11.

Only a few studies are available on repeated inhalation toxicity. In a limited study, two dogs were exposed for 6 months to about 10 mg/m³ hydrogen peroxide (one unexposed dog served as a control)11. The exposure obviously caused irritation of the skin (the animals rubbed certain areas of the skin hairless), eyes (lacrimation), and the nose (sneezing). Histopathological examination indicated that the skin was greatly thickened with a loss of hair, although hair follicles were not destroyed. The lungs exhibited patchy areas of atelectasis and emphysema, and the small terminal bronchioles and respiratory bronchioles had hyperplastic muscular coats. Scattered throughout the lung tissue, mainly where the alveolar walls seemed to be fragmented, there were circular areas composed of collagen, occasional muscle cells and strands of elastin11.

In the medical literature, there is a single case report of an interstitial lung disease in a 41-yr-old man exposed to hydrogen peroxide in a dairy12. He worked in an aseptic packaging line where the measured mean airborne level was 12 mg/m³ with short peaks up to 41 mg/m³. The patient had smoked heavily (about 2 packs cigarettes per day) for 25 yr. At work he had noticed, like his 6 fellow workmen, eye and throat irritation and gradual bleaching of the hair. Within one month he developed increasing dyspnea, and in a radiological examination diffuse nodular infiltrates were detected in both lungs. Extensive investigations including a transbronchial biopsy of the lung led to the diagnosis of interstitial lung disease. Withdrawn from occupational exposure, the patient improved progressively without treatment, and by one and a half months he no longer experienced dyspnea. After subsequent oral corticosteroid medication the chest radiograph and lung function tests normalised. After careful differential diagnostic considerations the authors attributed the clinical condition to the high hydrogen peroxide exposure. Heavy smoking may have been a contributing factor.

The sensitivity of the respiratory organs to oxidising gases such as hyperbaric oxygen and ozone are well
known. In aerobic cells hyperoxia increases the generation of reactive oxygen species, primarily superoxide anion and hydrogen peroxide, which adversely affect the lungs\(^1\). Ventilation with 100% oxygen for 4–12 h caused irritation in the throat, chest pain and coughing in sensitive individuals, and bronchoscopy of volunteer subjects after 6 h of exposure showed clinical tracheobronchitis\(^1\). If exposure is continued further, more severe injury may develop including diffuse alveolar injury: accumulation of neutrophils in the interstitial tissue and the alveoli, alveolar oedema and, in the worst case, adult respiratory distress syndrome (ARDS) with permanent sequelae\(^1\, 2\).

Ozone even at low levels (about 0.2 mg/m\(^3\)) already induces mild irritation in the eyes and the respiratory system, accumulation of inflammatory cells in mucous membranes, and reversible changes indicative of obstruction of small airways, but humans become adapted when exposed repeatedly\(^2\, 3\). At about five times higher levels, which may be encountered in the work environment, ozone causes smarting in the eyes, nose and throat, mucosal dryness and a dry cough. Welders exposed to ozone have exhibited bronchial hyperreactivity\(^4, 5\). Oxidants such as ozone may aggravate the symptoms of asthmatics\(^6, 7\), or may impair the immune response and increase susceptibility to respiratory infections\(^8\). Even chronic effects of oxidants on the respiratory system are considered possible, although so far there is little evidence of it\(^2, 3\).

There are close similarities among the symptoms caused by oxidant gases in humans and the symptoms which we detected in workers exposed to hydrogen peroxide vapours. Our investigation was based on existing medical documents and no examinations were performed to explore specific changes in the lungs. Therefore, we cannot draw definite conclusions about chronic effects of peroxide in the lungs, although they seem unlikely, as the patients monitored in the study regained good health after exposure was reduced. Our findings on respiratory morbidity support the hypothesis that repeated exposure to high levels of \(\text{H}_2\text{O}_2\) vapour induces sustained irritation and inflammation of the airway mucosa and increase susceptibility to respiratory infections, which moreover tend to become complicated and prolonged. In addition, two patients developed bronchoconstriction which required medication, and one of the two showed signs of slight nonspecific bronchial hyperreactivity. These may be early signs of irritant induced asthma or RADS (reactive airways dysfunction syndrome)\(^9\) although so far there is no unequivocal evidence that low-level irritation does cause asthma.

Among the symptomatic workers, antibiotics produced a favourable response in the treatment of bronchitis and sinusitis but cough and headache continued for a long time. The protracted infections and daily symptoms of irritancy and headache disappeared when the working conditions improved. It should be noted that three other heavily exposed workers reported little or no symptoms in the questionnaire, and did not exhibit morbidity. Hence individual susceptibility to peroxide induced irritation must vary. One of the symptomatic patients three decades earlier had repeated middle ear infections leading to mastoidectomy and myringoplasty in both ears. The first of our two cases did not have any significant previous lung disorders. The other case, who was younger and a smoker, had no previous respiratory diseases that would explain increased susceptibility. He was examined about one year after his work-related airway symptoms for an antibody response indicative of past chlamydial or mycoplasma infection, but the findings were negative. Among healthy volunteers 10–20 per cent were shown to be more sensitive than average to the respiratory effects of ozone\(^1\). The underlying mechanisms are not well elucidated but asthmatics belong to the susceptible population.

Although hydrogen peroxide is widely used e.g. for disinfection there are no reliable data concerning the chronic effects of its vapour. Occupational health personnel at the fruit juice factory under study suspected that respiratory symptoms and recurrent infections were linked to peroxide exposure. The study findings indicate that airborne peroxide levels clearly in excess of the current occupational exposure limit adopted in many countries (1.4 mg/m\(^3\)) indeed cause irritation in the upper and lower airways. The findings even supported the hypothesis of a link between peroxide exposure, recurrent infections and asthmatic symptoms, although the results must be viewed with caution because of the few individuals involved. To safeguard the health of workers it is important that hygienic measures in aseptic packaging limit the air levels of hydrogen peroxide to less than the occupational exposure limit.

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