



Department for Work and Pensions

Department for Work and Pensions Social
Security Administration Act 1992

Bronchiolitis Obliterans and Food Flavouring Agents

**Report by the Industrial Injuries Advisory Council
in accordance with Section 171 of the Social Security
Administration Act 1992 reviewing prescription
for Bronchiolitis Obliterans and food flavouring
agents**

*Presented to Parliament by the Secretary of State for Work and Pensions
By Command of Her Majesty
July 2008*



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INDUSTRIAL INJURIES ADVISORY COUNCIL

Secretary of State for Work and Pensions

Dear Secretary of State,

REVIEW OF BRONCHIOLITIS OBLITERANS AND FOOD FLAVOURING AGENTS

This report details the Council's consideration of prescription for bronchiolitis obliterans arising from exposure to food flavouring agents containing diacetyl (referred to in early research reports as 'popcorn worker's lung').

Evidence of an association was first brought to our attention in November 2007 by colleagues from the Health and Safety Executive. We have since considered published research on the topic, made a call for evidence and consulted with experts in the field, and present our recommendations to you within eight months of commencing the review. The expediency with which we have completed our report is, in part, due to our wish to raise awareness of this uncommon and very harmful respiratory condition so that cases may be recognised, where appropriate compensated and ultimately be prevented.

A body of evidence is emerging that links exposure to certain food flavouring agents, notably the buttery food flavouring agent diacetyl, with the development of bronchiolitis obliterans. Several cases have been reported in the USA and in Europe, including one from the UK, in workers exposed to diacetyl-containing food flavouring agents, used in popcorn and potato crisp manufacture, and in the production of diacetyl. The toxic injury this agent can cause to the lungs has been confirmed in animal experiments, which add to the epidemiological evidence in human populations. Bronchiolitis obliterans is a rare disease, so in affected individuals whose work involves exposure to food flavouring agents containing diacetyl, an occupational cause can be strongly presumed.

We recommend that bronchiolitis obliterans arising during work involving the production of diacetyl, or the manufacture of food flavourings containing diacetyl, or the manufacture of food flavoured by diacetyl be added to the list of prescribed diseases for which Industrial Injuries Disablement Benefit is payable.

Yours sincerely,

Professor K Palmer

Chairman

Date: July 2008

Summary

1. Bronchiolitis obliterans is an uncommon respiratory disease characterised by fixed airway obstruction, whereby the bronchioles in the lung become narrowed or blocked by fibrous tissue. The disease is disabling and can be potentially severe, leading to lung transplantation in some patients. Bronchiolitis obliterans may be caused occupationally by accidental, acute, high concentration exposure to industrial gases, such as nitrogen dioxide.

2. In November 2007, the Council's attention was drawn to emerging evidence of an association between bronchiolitis obliterans and day to day exposure to food flavouring agents (i.e. not linked with accidental chemical exposures). Cases were first identified in workers exposed to food flavouring agents used in popcorn manufacture in the United States, and the disease became known as 'popcorn worker's lung'. Subsequently, however, cases were identified outside popcorn manufacture, in manufacture of the food flavouring agent, diacetyl (also known as butanedione or 2,3-butanedione; C₄H₆O₂), in the Netherlands, and in potato crisp production in the UK. Evidence suggests that the causal agent is likely to be diacetyl, an agent with a buttery flavour, or a chemical closely associated with diacetyl usage or production.

3. Following reviews of relevant research, calls for evidence and consultations with experts in the field, the Council concludes that a causal relationship between bronchiolitis obliterans and exposure to food flavouring agents is likely, and is supported by i) evidence of the clustering of cases of this rare disease in several factories where exposures to diacetyl were shared in common; ii) the development of fixed airways obstruction in the absence of other explanations (e.g. emphysema); iii) a demonstrated dose-response relationship between exposure to food flavouring agents and the onset of symptoms and declining lung function, and iv) experiments demonstrating pulmonary damage in animals exposed to diacetyl. The Council has concluded that there is strong evidence of an association between work in diacetyl production or use of diacetyl as a food flavouring agent and the development of bronchiolitis obliterans.

4. Diagnosis of bronchiolitis obliterans is relatively complicated, based on clinical features, lung function tests, chest radiographs and computed tomography scans. A feature that distinguishes bronchiolitis obliterans from the more chronic condition of bronchitis and emphysema, however, is the relatively rapid onset of symptoms (within weeks or months) following diacetyl exposure, as compared to the much slower progression of symptoms associated with the development of chronic airways disease.

In practice, cases presenting for benefit are likely to have had extensive clinical investigations to confirm diagnosis.

5. The Council recommends that bronchiolitis obliterans arising during work involving production of diacetyl, or the manufacture of food flavourings containing diacetyl, or the manufacture of food flavoured by diacetyl be added to the scheduled list of prescribed diseases for which Industrial Injuries Disablement Benefit is payable. Diagnosis should normally be based upon prior hospital investigations, and confirmatory evidence of diagnosis should be sought from the appropriate source(s).

INTRODUCTION

Background to this review

6. In November 2007, Health and Safety Executive officials highlighted to the Council emerging research literature about workers in North America with bronchiolitis obliterans exposed to flavouring agents used in the food processing industry. The term 'Popcorn worker's lung' was coined to describe the disease as the clusters of cases reported in North America were first described in workers in microwave popcorn processing plants. The Council's enquiries also identified one case of bronchiolitis obliterans in the United Kingdom associated with occupational exposure to food flavouring agents used in potato crisp manufacture (Hendrick, 2008).

Method of investigation

7. IIAC referred the matter of food flavourings and bronchiolitis obliterans to its permanent sub-committee, the Research Working Group, which conducted a literature search and reviewed key research papers. The Council also consulted with a respiratory expert about diagnostic criteria for bronchiolitis obliterans, and made a call for evidence on its website and through the specialist Society of Occupational Medicine and a respiratory physicians' reporting network (Appendix 1).

Bronchiolitis obliterans – the disease

8. Bronchiolitis obliterans is a rare and sometimes severe respiratory disease where inflammation and fibrosis lead to airflow limitation in the small airways of the lung. The disease can be life-threatening and some patients may require lung transplantation.

9. Bronchiolitis obliterans is characterised by fixed airways obstruction, whereby bronchioles in the lung become blocked or narrowed by fibrous tissue associated with wound healing (granulation). Bronchioles are small airways which extend from the larger conducting airways of the bronchi to the alveoli (the gas exchanging parts of the lung) (see Figure 1). Patients with bronchiolitis obliterans have reduced lung function and typically have dry cough, undue shortness of breath upon exertion and occasionally, wheezing.

10. Several other respiratory diseases, such as asthma, bronchitis and emphysema, have similar clinical symptoms to bronchiolitis obliterans, with potential for misclassification. However, a characteristic point of distinction between bronchiolitis obliterans and chronic obstructive airways disease is the far more rapid onset and time course of symptoms in the former (weeks or months and less than a year) in contrast to the slow and insidious onset of breathlessness in the latter.

11. Diagnosis of bronchiolitis obliterans may involve a variety of test modalities – spirometry and other lung function tests, high resolution computed tomography (HRCT), chest radiographs and lung biopsy. Affected individuals often have severe airways obstruction on spirometry that is unresponsive to treatment with bronchodilator medication (fixed airways obstruction). Lung volumes are typically reduced. Chest radiographs may show hyperinflation in some but not all cases. Due to sampling errors, lung biopsies may also appear normal. HRCT is considered the most helpful means of diagnosing the disease. Characteristically, this shows a mosaic pattern of pulmonary lobules during inspiration, air trapping (hyperinflation) during expiration, irreversible patchy fibrosis, causing the walls of less involved bronchioles to be pulled outwards (so-called ‘traction bronchiectasis’), mucus plugging, airway wall thickening and solidification of the normally soft, aerated lung tissue (consolidation).

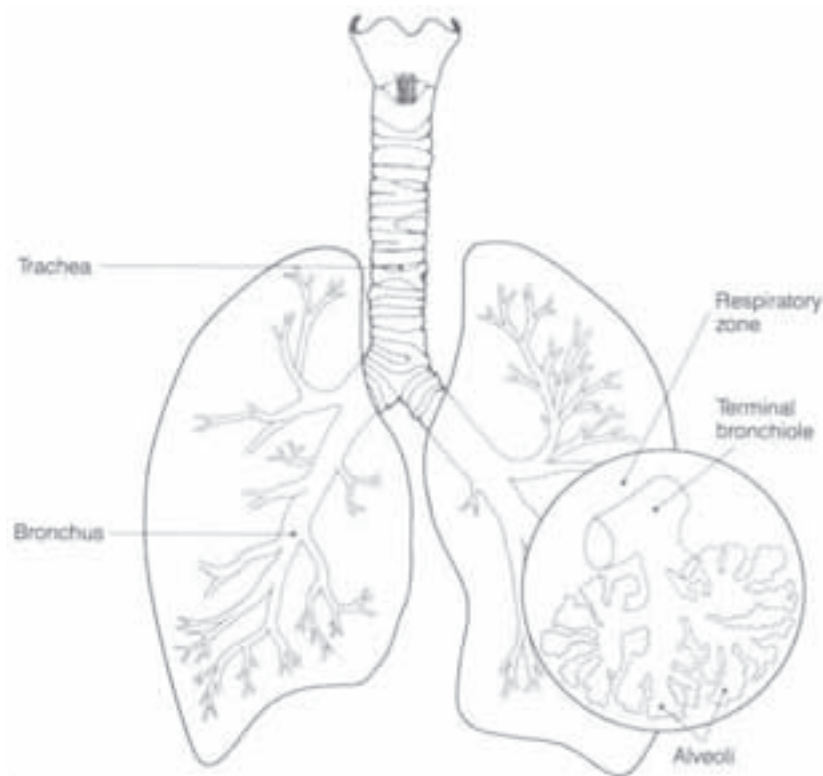


Figure 1. Diagram of the lungs showing the airways and respiratory zone. Air passes through the trachea, bronchi and bronchioles to alveoli which arise from terminal bronchioles. The exchange of oxygen and carbon dioxide occurs in the alveoli. Diagram taken from Cotes and Steel, ‘Work related lung disorders’ and reproduced with kind permission of Blackwell Scientific Publications Ltd.)

12. Non-occupational causes of bronchiolitis obliterans include viral infections, rheumatoid disease, organ transplant rejection and adverse drug reactions. Cases of occupational bronchiolitis obliterans have been reported in connection with acute exposure to high concentrations of industrial gases, including nitrogen dioxide, sulphur dioxide, phosgene, ammonia, chlorine and methyl isocyanate (as occurred in the Bhopal disaster in 1984).

13. The association between bronchiolitis obliterans and chemical agents associated with food flavouring differs from occupational instances in paragraph 12 in that cases have developed after exposures occurring from routine use of the agents in question, rather than from high concentrations arising from accidental chemical spills (in principle, illnesses arising from such accidental exposures would fall within the accident provisions of the Scheme).

Evaluation of the research literature relating to bronchiolitis obliterans

14. In May 2000, the National Institute of Occupational Safety and Health (NIOSH) in USA was alerted to eight cases of severe airways obstruction in workers from a microwave popcorn factory. Five of the cases were on lung transplantation lists. An occupational causation was suspected as the cluster of cases had severe airways obstruction, occurred at relatively young ages (age range 27-51 years; median 41 years), mostly among workers who had never smoked or who had all worked in one small plant. The cases were employed in the factory for between 1 and 17 years (median duration 2 years) and none had acute, high chemical concentration exposures before the onset of symptoms. The workers reported symptoms after working at the factory for a median duration of 1.5 years (range 5 months – 9 years). Detailed medical investigations indicated that eight of the cases had bronchiolitis obliterans and had had exposures to chemicals involved in the flavouring of microwave popcorn (Akpinar-Elci *et al.*, 2004). A principal component of these chemicals is diacetyl, a ketone with butter flavouring characteristics, and it was postulated that diacetyl caused bronchiolitis obliterans in these workers (or was a marker for exposure to other closely related food flavouring agents that had a causal relationship to disease).

15. Half of the cases had worked in a mixing room where the flavouring components were combined with heated soybean oil and the remainder worked in the microwave packaging area. Later hygiene measurements suggested that workers in the mixing room were exposed to a geometric mean air concentration of diacetyl of 18 parts per million (ppm), and those in the microwave packaging area were exposed to 1.3ppm, representing high levels of exposure compared with other areas in the factory (0.02ppm).

16. The reporting of this case series prompted experimental studies in rats, conducted by the Centre for Disease Control (CDC) in North America. These added to the biological plausibility of a causal association by showing that inhalation of butter flavourings used at the plant, and diacetyl in particular, could cause severe airways damage in animal models (MMWR, 2002).

17. Further local investigations followed. A cross-sectional medical and hygiene survey at the plant showed that the workforce had an excess prevalence of respiratory symptoms compared with a reference population (2.6-fold greater prevalence of chronic cough and shortness of breath upon

exertion; 3-fold greater prevalence of wheezing) (Kreiss *et al.*, 2002). The relative risks of these symptoms were higher among those who had never smoked than in current or former smokers, and were higher amongst younger workers (17-39 years) than older workers (40-69 years). The overall prevalence of airways obstruction was over 3 times higher than the expected rate, and increased by some 8-11 fold in those who had never smoked. A strong association was found between estimated cumulative exposure to diacetyl and the frequency and extent of airways obstruction. Microwave popcorn production workers had higher rates of respiratory symptoms than minimally exposed workers who worked in non-flavoured popcorn production, such as office and warehouse areas. Workers who mixed the popcorn and flavour components together in the mixing room also had an increased rate of job change attributed to their respiratory symptoms. The authors believed that many workers with airways obstruction were suffering from bronchiolitis obliterans.

18. Further cases of bronchiolitis obliterans were reported from other flavouring and food production factories across North America (Kanwal *et al.*, 2006; MMWR, 2007), and in five of six microwave popcorn plants (including the original plant) investigated by Kanwal *et al.*, evidence was found of excesses of respiratory symptoms and fixed airways obstruction. Such symptoms arose this time in the context of apparently low concentrations of diacetyl (geometric air concentrations were as low as 0.02 ppm in mixing rooms with established cases).

19. Cases of bronchiolitis obliterans have also been identified in chemical workers producing diacetyl for use by food producers in The Netherlands (van Rooy *et al.*, 2007). That these recent cases have occurred in diacetyl production, rather than in microwave popcorn production, adds strongly suggestive evidence that diacetyl (or an agent involved closely in its production or use) is a causative agent in the development of bronchiolitis obliterans.

20. Affected workers in index reports have presented with severe airways obstruction on spirometry that proved unresponsive to treatment with bronchodilator medication. Lung volumes were typically reduced. In affected workers from the popcorn factories, the forced expiratory volume in one second (FEV1) measurement was only at 17-44% of that expected given their age and sex. In affected workers involved in the production of diacetyl, FEV1 measurements were 31-42% of predicted values.

The case for prescription

21. When considering the case for prescription of a disease and its occupational exposure, the Council must adhere to statutory requirements (see Appendix 2). Briefly, a disease may only be prescribed if there is a

recognised risk to workers in an occupation, and the link between disease and occupation can be established or reasonably presumed in the individual case. Where the clinical features of a case are not specific to occupation, the Council looks for evidence of work causation “on the balance of probabilities” (earlier reports explain how this equates in epidemiological terms to a more than doubling of risks in the occupational group in question). However, in some circumstances attribution is possible on the basis of specific clinical features of the disease, and more rarely the disease only arises from occupation or specific occupational activities. One recent example in which the Council recommended prescription on the basis of clinical features of the disease is extrinsic allergic alveolitis due to exposure to mists from metal working fluid (‘Extrinsic Allergic Alveolitis’ Cm. 6867, July 2006).

22. Similarly, the case for prescription in bronchiolitis obliterans can be made on the basis of specific clinical features. The collective evidence on this topic suggests that diacetyl, or closely a related food flavouring, is a cause of bronchiolitis obliterans. This view is supported by (i) the clustering of cases of this rare disease in close proximity to this shared common exposure; (ii) the occurrence of severe respiratory disease of fairly rapid onset in the absence of other explanations (e.g. in non-smokers); (iii) the dose-response pattern of symptoms and airways obstruction; and (iv) the experimental evidence that diacetyl can cause pulmonary damage in animal inhalation models. Cases have occurred in workers manufacturing diacetyl as well as in those using it as a food flavouring in popcorn production. This strengthens the case that diacetyl itself is the aetiological agent, although not excluding the possibility that it is also a marker of exposure to an associated causative agent.

23. Given the rarity of this respiratory disease in working populations, occurrence of a case in a worker producing diacetyl or employing it in food processing and food flavouring operations is, of itself, strong grounds for presuming occupational attribution in the individual case. As outlined in paragraph 10, the far more rapid onset and time course of symptoms and declining lung function in bronchiolitis provides a point of contrasts with the more insidious course of other chronic obstructive pulmonary diseases.

24. The disease warrants prescription in that disease can be severely disabling, sometimes leading to lung transplantation. Although bronchiolitis obliterans may stabilise in some workers who are removed from the exposure, in others it may worsen.

25. Diagnosis for bronchiolitis obliterans is relatively complicated, due to the clinical and pathological overlap with other respiratory conditions such as emphysema (Kanwal, 2008). However, it is unlikely that a person will be

diagnosed with the condition without having undergone careful hospital investigation. It is recommended that confirmatory evidence of diagnosis be sought from the appropriate expert source(s).

26. The Council was advised that traditional lung function tests are suitable and helpful measures in assessing the disablement arising from bronchiolitis obliterans.

27. Based on the balance of evidence, the Council concludes there is strong evidence of an association between work in diacetyl production or use of diacetyl as a food flavouring agent and the development of bronchiolitis obliterans.

28. Physicians should consider a diagnosis of bronchiolitis obliterans in patients presenting with severe fixed airways obstruction of acute or subacute onset and an occupational history of exposure to diacetyl in food production or manufacture.

Prevention

29. Bronchiolitis obliterans arising from work exposure is a preventable illness. The Control of Substances Hazardous to Health Regulations 2002 (as amended) (COSHH) apply to work with hazardous substances such as diacetyl. These regulations require that work is not carried out with any substance liable to be hazardous to health unless a suitable and sufficient assessment has been made of the risks created by the work and measures are taken to prevent exposure as far as is reasonably practicable. Where it is not reasonably practicable to prevent exposures by substitution with a safer substance or total enclosure, exposure must be adequately controlled by the use of appropriate work processes, systems and engineering controls and measures, including local ventilation systems, to control exposures at source. Suitable respiratory protective equipment may be used in addition, where adequate control cannot otherwise be achieved. Workers handling diacetyl need to be informed of the hazards/risks and be provided with appropriate training. In addition COSHH requires employers to arrange appropriate health surveillance for bronchiolitis obliterans where employees are exposed to a substance known to cause it, and there is a reasonable likelihood of the disease occurring under the conditions of the work.

Recommendations

30. The Council recommends prescription for bronchiolitis obliterans for workers involved in diacetyl production or use of diacetyl as a food flavouring agent as shown in the table below.

Prescribed disease	Occupation
C31 Bronchiolitis obliterans	Work involving the production of diacetyl, or the manufacture of food flavourings containing diacetyl, or the manufacture of food flavoured by diacetyl .

31. Diagnosis of bronchiolitis obliterans will normally be based upon hospital investigations and confirmatory evidence of diagnosis should be sought from the appropriate expert source(s).

APPENDIX 1:

Experts consulted

Dr Chris Stenton (Consultant respiratory physician), University of Newcastle

Professor David Hendrick (consultant respiratory physician), University of Newcastle

Calls for evidence were placed on the IIAC website, with the newsletter of the Society of Occupational Medicine UK, and sent to British chest physicians through the coordinator of the SWORD national network of reporters.

APPENDIX 2: The Legal Requirements for Prescription

The Industrial Injuries Disablement Benefit Scheme

32. The Industrial Injuries Disablement Benefit (IIDB) scheme provides non-contributory, 'no-fault' benefits for disablement because of accidents or prescribed diseases which arise during the course of employed earners' employment. The benefit is paid in addition to other incapacity and disability benefits. It is tax-free and administered by the Department for Work and Pensions.

The Role of the Industrial Injuries Advisory Council

33. IIAC is an independent statutory body established in 1946 to advise the Secretary of State for Social Security on matters relating to the IIDB scheme. The majority of the Council's time is spent considering whether the list of prescribed diseases for which benefit may be paid should be enlarged or amended.

The legal requirements for prescription

34. The Social Security Contributions and Benefits Act 1992 states that the Secretary of State may prescribe a disease where he is satisfied that the disease:

- a) ought to be treated, having regard to its causes and incidence and any other relevant considerations, as a risk of the occupation and not as a risk common to all persons; and
- b) is such that, in the absence of special circumstances, the attribution of particular cases to the nature of the employment can be established or presumed with reasonable certainty.

35. In other words, a disease may only be prescribed if there is a recognised risk to workers in an occupation, and the link between disease and occupation can be established or reasonably presumed in individual cases.

36. In seeking to address the question of prescription for any particular condition, the Council first looks for a workable definition of the disease. The Council then searches for a practical way to demonstrate in the individual case that the disease can be attributed to occupational exposure with reasonable confidence. For this purpose, reasonable confidence is interpreted as being based on the balance of probabilities according to the available evidence in the scientific literature. An accident at work is specifically catered for within the IIDB scheme. However, if the condition might result from occupational exposure in the absence of an identifiable accident, the Council must consider whether it should be included in the list

of diseases that are prescribed for benefit purposes. In these circumstances, it may be possible to ascribe a disease to a particular occupational exposure in two ways – from specific clinical features of the disease or from epidemiological evidence that the risk of disease is at least doubled by the relevant occupational exposure.

Clinical features

37. For some diseases attribution to occupation may be possible from specific clinical features of the individual case. For example, the proof that an individual's asthma is caused by his occupation may lie in its improvement when s/he is on holiday and regression when s/he returns to work, and in the demonstration that s/he is allergic to a specific substance with which s/he comes into contact only at work. It can be that the disease only occurs as a result of an occupational hazard (e.g. coal workers' pneumoconiosis).

Doubling of risk

38. Other diseases are not uniquely occupational, and, when caused by occupation, are indistinguishable from the same disease occurring in someone who has not been exposed to a hazard at work. In these circumstances attribution to occupation on the balance of probabilities depends on epidemiological evidence that work in the prescribed job, or with the prescribed occupational exposure, increases the risk of developing the disease by a factor of two or more. In the case of chronic bronchitis and emphysema the criteria for prescription were that there needed to be evidence of a greater than doubled risk of a disabling loss of lung function in exposed compared with unexposed workers. The requirement for, at least, a doubling of risk is not arbitrary. It follows from the fact that if a hazardous exposure doubles risk, for every 50 cases that would normally occur in an unexposed population, an additional 50 would be expected if the population were exposed to the hazard. Thus, out of every 100 cases that occurred in an exposed population, 50 would do so only as a consequence of their exposure while the other 50 would have been expected to develop the disease, even in the absence of the exposure. Therefore, for any individual case occurring in the exposed population, there would be a 50% chance that the disease resulted from exposure to the hazard, and a 50% chance that it would have occurred even without the exposure. Below the threshold of a doubling of risk only a minority of cases in an exposed population would be caused by the hazard and individual cases therefore could not be attributed to exposure on the balance of probabilities. The epidemiological evidence required should ideally be drawn from several independent studies, and be sufficiently robust that further research at a later date would be unlikely to overturn it.

39. The evidence on bronchiolitis obliterans and occupational exposure to diacetyl is such that attribution can be made in the individual case on the basis of the clinical features.

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