HSE

Health and Safety Executive

Asthmagen?

Critical assessments of the evidence for agents implicated in occupational asthma

First published 1997, reprinted with amendments 1998, 2001

SECTION A: Forword

In HSE the process of critical appraisal of toxicological information has been undertaken for a number of years within regulatory programmes associated with the classification of industrial chemicals and the setting of occupational exposure limits. The resulting assessments provide the basis for the individual entries in this compendium. It should be noted that when full information regarding the potential of a substance to cause asthma has already been (or is expected to be) published by HSE elsewhere, eg in a criteria document or risk assessment document, the compendium entry consists of a summary of that information, together with a reference to the original publication.

Overall, it is clear that all the relevant information available for each substance needs to be carefully examined against accepted criteria. Proper application of these criteria requires a balance of judgment, with the quality of the available data as well as the numbers of cases (in relation to the size of the exposed population and extent of exposure) being taken into account in order to reach the most reliable assessment of the potential to produce respiratory sensitisation/asthma.

The compendium originally comprised 32 such assessments when it was published in 1997, reported in a standard format and arranged alphabetically by common name. A further 12 assessments were added with publication of a Supplement in 1998. The 2001 Supplement comprises an additional 16 assessments.

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SECTION B: Introduction

Purpose of the document

In 1993 the Health and Safety Commission (HSC) identified six health concerns related to occupational exposure to chemicals as priorities for action, one of which was occupational asthma (asthma caused by occupation). A number of sources of information show that occupational asthma, resulting from the inhalation of certain chemicals and other agents in the workplace, has become a major category of work-related respiratory ill-health in the UK. These sources include data from the Labour Force Survey (Hodgson *et al*., 1993) and the Surveillance of Work-related and Occupational Respiratory Disease (SWORD) scheme, funded by HSE (Meredith *et al*., 1991). This increased prominence is due, among other factors, to a decline in more traditional occupational diseases such as bronchitis, byssinosis and pneumoconiosis, and to the increased industrial use of reactive chemicals, which can have asthmagenic properties.

In response to HSC's recommendations, the Health and Safety Executive (HSE) in 1994 published specific guidance about prevention of occupational asthma, with particular emphasis on compliance with the Control of Substances Hazardous to Health (COSHH) Regulations (HSE, 1994). This guidance expands on the relevant parts of the COSHH Regulations and provides practical advice in the form of check-lists and case studies.

There are two elements to the occurrence of asthma in an individual. One is the induction (or initiation) of the condition, which involves the rendering of the airways unusually sensitive (hypersensitive), so that subsequent environmental conditions or situations may produce a reaction of the airways that would not otherwise have occurred. The other element is the actual elicitation (or provocation) of such a reaction, usually manifested as the classical "chest-tightening" symptoms of asthma. The elicitation of an asthmatic response in hypersensitive airways can be very specific to a particular agent, but the airways can also become unusually responsive to a wide range of common external factors, including general dustiness, cold air, exercise and stress. Such commonly occurring environmental conditions are not amenable to effective regulatory control; the regulatory strategy is aimed at preventing the production of the hypersensitive state.

From a regulatory perspective, a "cause" of occupational asthma is considered to be an agent which both produces the hypersensitive state in the airways and triggers a subsequent reaction in those airways. Hence, key to the prevention of occupational asthma is provision of a clear authoritative statement identifying which substances are capable of causing occupational asthma ("asthmagens") and should be subject to the controls given in the guidance. This was not available when the guidance was published, but in order to provide some information to guide employers two lists were included in the document. The first list comprises agents responsible for most cases of occupational asthma in the UK, as indicated by the findings of the SWORD surveillance scheme. The second list gives some other agents for which there are one or more reports in the scientific and medical literature alleging that they cause occupational asthma. (In the Guidance the agents are listed as having the potential to cause occupationally-related "respiratory sensitisation". The overlap and confusion in terminology is discussed below). However, the strength of evidence that the agents in this second list can cause occupational asthma is very variable. Naturally, HSE wishes to see those agents with clear asthmagenic (asthma-causing) properties tightly controlled. On the other hand, it is undesirable and counterproductive to have the same image and control regime applied to agents for which the evidence for asthmagenicity (the property of causing asthma) is ill-founded. Consequently, it was apparent that, particularly for agents in the second list, there was a need to assess critically the toxicological information underpinning the suggestion that they could cause occupational asthma. That is the purpose of this document. It comprises summaries derived from critical appraisal of the available toxicological evidence surrounding the asthmagenic potential of substances, and includes substances for which the balance of evidence indicates that they should not be considered to be asthmagens as well as those that should. The information will help employers

and occupational health professionals in carrying out assessments under the COSHH Regulations.

It is fair to say that substance-related asthma has proved over recent years to be one of the more difficult and controversial areas of regulatory toxicology. The development of clear positions has been hampered by a lack of understanding of underlying toxicological mechanisms, the confusion of terminology, the absence of internationally accepted experimental test systems, inconclusive clinical data and doubt concerning the impact on the risk of occupational asthma of different exposure patterns and routes. These problem areas are described below, in order to provide the context for the specific criteria that have recently emerged within the European Union (EU) to assist in the classification of chemicals with respect to their potential to cause asthma. These criteria are then described in detail. The critical assessments of the available toxicological information relating to asthmagenicity that form the individual compendium entries have each been considered against the new EU classification criteria, in order to reach a conclusion on the potential of each agent to cause asthma. It should be noted that although the classification criteria have direct regulatory application only to chemicals that are supplied on the EU market, for the purposes of this compendium they have also been applied during the assessment of a number of substances of biological origin, and of solder fume.

Terminology and toxicological mechanisms

The varying and sometimes overlapping definitions available for key terms, such as hypersensitivity, respiratory sensitisation, allergy and asthma, constitute an important source of possible confusion. Medical, regulatory, industrial and academic scientists may each have their own understanding of the meaning of these terms. The terms “asthma” and “respiratory sensitisation” have been used synonymously and interchangeably by some in the occupational health field, but are distinguished from each other in some minds. This lack of clarity surrounding definitions has been compounded by uncertainties regarding the toxicological mechanisms underlying the disease processes involved in asthma. Thus, possible meanings for “respiratory sensitisation” in relation to effects in the lung include:

(a) asthma induced by a proven immunological mechanism;

(b) asthma induced by an immunological mechanism which may be proven or simply presumed;

(c) asthma induced by a mechanism specific to the substance in question, but which may be immunological or non-immunological; or

(d) asthma induced by any means.

A further possible refinement to these definitions is the differentiation of immunological mechanisms into those mediated by immunoglobulin E (IgE) and those apparently not. However, given the current rather rudimentary state of knowledge concerning the mechanisms underlying the production of asthma, particularly for many low molecular weight chemicals, with regard to the property of producing “respiratory sensitisation”, regulatory attention has focused on the potential for production of the disease of concern (i.e. asthma), without imposing any absolute requirement to elucidate the underlying toxicological mechanism. This approach has been adopted in the EU classification criteria developed to reflect the hazard “respiratory sensitisation” (production of asthma), as described below. Nevertheless, consideration of the potential underlying mechanism is an important factor in determining the appropriate risk management option(s) for any confirmed “respiratory sensitiser”/”asthmagen”. For instance, different approaches may be taken for substances producing asthma via immunological as against non-immunological mechanisms.

Methods for identification of asthmagens

A factor that makes the identification of agents having the ability to cause asthma less straightforward than for most other toxicological endpoints is the lack of a fully validated predictive animal test. Although a number of methods using guinea pig and mouse show considerable promise, none has yet attained international regulatory recognition as a test guideline adopted by the Organisation for Economic Co-operation and Development. The available methods are generally considered by regulators to be acceptable as screening tests, which can provide useful information for chemicals giving positive responses leading, for example, to classification and labelling. However, negative findings produced by these methods are not currently taken to be a reliable indicator of the absence of asthmagenic potential. Similarly, no standard, validated *in vitro* method is available, although the potential for a chemical to interact with protein can be considered a prerequisite for immunogenic activity. Another potential source of information, structure-activity relationship modelling, is still at a relatively early stage of development. Clearly, however, simple examination of molecular structure for reactive groups and checking whether a particular chemical is of a type (isocyanates or anhydrides, for example) already associated with the induction of asthma is worthwhile.

The absence of routinely-used animal and *in vitro* test methods means that much of the information available for an evaluation of the potential of chemicals and other agents to cause asthma is based on clinical and epidemiological findings in people exposed at the workplace or, occasionally, at home or elsewhere. In one sense such human data are ideal, in that they come directly from the species and biological system of interest. However, from the regulatory perspective this information can also suffer from a number of deficiencies, some deriving from the nature of the original purpose of the investigations. Many studies have been aimed at the clinical diagnosis of asthma in a patient without any particular need to identify stringently the agent responsible for inducing the state of airway hypersensitivity, as opposed to that simply provoking in a non-specific manner the asthmatic symptoms in an individual already having hypersensitive airways, for reasons known or unknown. Exposure data for the period leading up to the recognition of occupational asthma is rarely available, and in many cases unquantified, but possibly high, previous and/or concurrent exposures to agents other than the one under suspicion may serve to prevent a firm conclusion being drawn about which chemical/agent induced the hypersensitive state.

The clinical investigations themselves may contribute further uncertainty by the nature of their conduct and the interpretation of their findings. An example is provided by the bronchial challenge test, which is often considered to be the “gold standard” by regulators for the attribution of asthma to a specific agent. For such a test to be considered truly rigorous by regulatory standards, a series of conditions should be met, including use of a clearly sub-irritant concentration of the putative asthmagen, maintaining blind conditions for the subject (and preferably also for the investigator) to the nature of the exposure (i.e. whether to the test or control substance), and careful control of possible confounding factors, such as use of asthma medication, smoking habits and the existence of upper respiratory tract viral infection. For a positive result to be convincing for regulatory purposes, the response should be of an appropriate magnitude (e.g. a decrease in the forced expiratory volume in one second of 15% or greater) over and above any effect seen at the control challenge. Unfortunately, it is unusual for bronchial challenge tests reported in the scientific literature to me *et al*l or even most of these conditions, reflecting the fact that the tests are normally carried out for reasons of medical diagnosis of a condition rather than regulatory identification of a hazardous property of a specified agent.

Thus, in attempting to form an opinion about the asthmagenic potential of a substance it is often the case that a balanced view of all the information available needs to be taken in order to make the best scientific judgement possible.

Other risk management issues

An important and as yet unresolved issue concerns the significance of peak exposures in the induction of the hypersensitive state. Such peaks, consisting of brief periods (perhaps of less than a minute) of exposure to high concentrations of the agent, may be masked in 8-hour time-weighted average values for exposure derived by routine personal sampling, but in fact reflect the intermittent nature of exposures in many industrial processes. At the present time practical experience in several industries suggests that peak exposures are important in the induction of the hypersensitive state, although the scientific evidence remains inconclusive (Morris, 1994).

For chemicals which cause asthma there is also some uncertainty regarding the relevant routes of exposure for the induction phase of the process (i.e. rendering the airways hypersensitive). Regarding the provocation phase (i.e. triggering the airway reaction), clearly the inhalation route is generally the only relevant one. For protein and other macromolecular asthmagens, it is likely that inhalation is also the only route involved at the induction phase, as skin penetration is unlikely. In the case of low molecular weight chemicals, however, there is some evidence from animal studies that an immune response sufficient to sensitise the respiratory tract may occur after dermal exposure (Kimber and Wilks, 1995). The current regulatory view accepts that for a limited number of chemicals there is some indication from animal experiments that a hypersensitive state in the respiratory tract can be induced by skin contact. However, it may be that this is simply an experimental phenomenon rather than a reflection of a route that operates in exposed workers.

The EU classification criteria for respiratory sensitisation

A crucial starting point within the UK/EU framework for regulation of industrial chemicals is the identification of their hazardous properties. The classification system in place in the EU serves to identify the hazardous properties of chemicals which are supplied commercially, and the correct application of the system is a statutory requirement within each of the member states. Criteria used to derive the appropriate classification for a substance are available in Annex VI to the Dangerous Substances Directive, commonly referred to as the “labelling guide” (EEC, 1993). In the UK, the EU requirements are currently implemented by the Chemicals (Hazard Information and Packaging for Supply) Amendment Regulations 1996, commonly known as “CHIP 96” (DoE, 1996), and an “approved guide” containing the EU criteria is available (HSC, 1994).

Determining that a substance warrants classification as a respiratory sensitiser results in the assignment of the classification category “sensitising” and justifies application of the warning phrase R42 (may cause sensitisation by inhalation). However, there has been a problem in that the guidance given in the current EU labelling guide with respect to “sensitisation by inhalation” is not particularly helpful. Application of these very brief and rather general criteria led to a total of 23 individual substances being assigned R42 and listed in Annex I to the Dangerous Substances Directive. This annex is a compilation of several thousand agreed classification and labelling entries and is represented in the UK by the Approved Supply List (HSC, 1996). To improve the situation, new and more extensive criteria for the assignment of R42 were developed and formally adopted by EU member states in May 1996, with an intention that they come into effect in national law by 31 May 1998. The revised criteria were officially published in September 1996 (EC, 1996), and in the UK they will be incorporated in a revision of the CHIP Regulations in 1998. The new criteria and their supporting notes are reproduced in the boxes below, as it is against these that the critically appraised evidence on each of the agents covered in this compendium has been compared.

Sensitisation by inhalation

Substances and preparations shall be classified as sensitising and assigned the symbol ‘Xn’, the indication of danger ‘Harmful’ and the risk phrase R42 in accordance with the criteria given below:

R42 May cause sensitisation by inhalation

- if there is evidence that the substance or preparation can induce specific respiratory hypersensitivity
- where there are positive results from appropriate animal tests
- if the substance is an isocyanate, unless there is evidence that the substance does not cause respiratory hypersensitivity

Comments regarding the use of R42

Human evidence

Evidence that the substance can induce specific respiratory hypersensitivity will normally be based on human experience. In this context, hypersensitivity is normally seen as asthma, but other hypersensitivity reactions such as rhinitis and alveolitis are also considered. The condition will have the clinical character of an allergic reaction. However, immunological mechanisms do not have to be demonstrated.

When considering the evidence from human exposure, it is necessary for a decision on classification to take into account in addition to the evidence from the cases:

- the size of the population exposed
- the extent of the exposure

The evidence referred to above could be

- clinical history and data from appropriate lung function tests related to exposure to the substance, confirmed by other supportive evidence which may include:
    - a chemical structure related to substances known to cause respiratory hypersensitivity
    - in vivo immunological test (e.g. skin prick test)
    - in vitro immunological test (e.g. serological analysis)
    - studies that may indicate other specific but non-immunological mechanisms of action, e.g. repeated low-level irritation, pharmacologically mediated effects
- data from positive bronchial challenge tests with the substance conducted according to accepted guidelines for the determination of a specific hypersensitivity reaction.

Clinical history should include both medical and occupational history to determine a relationship between exposure to a specific substance and development of respiratory hypersensitivity. Relevant information includes aggravating factors both in the home and workplace, the onset and progress of the disease, family history and medical history of the patient in question. The medical history should also include a note of other allergic or airway disorders from childhood, and smoking history.

The results of positive bronchial challenge tests are considered to provide sufficient evidence for classification on their own. It is, however, recognized that in practice many of the examinations listed above will already have been carried out.

Substances that elicit symptoms of asthma by irritation only in people with bronchial hyper-reactivity should not be assigned R42.

Animal studies

Data from tests, which may be indicative of the potential of a substance to cause sensitisation by inhalation in humans, may include:

- IgE measurements (e.g. in mice)

- Specific pulmonary responses in guinea pigs

The second paragraph of these comments is intended to produce a distinction between the possession by a substance of any degree of ability, however weak, to produce respiratory sensitisation and the identification of a substance as having a significant sensitising potential. Only the latter type of substance warrants classification as a respiratory sensitiser and application of R42. This principle has been introduced in order to prevent a substance being classified on the basis of only one or two rare, idiosyncratic reactions, since there may be the possibility of this occurrence for very many substances. The key point is that the decision on classification needs to set the number of cases reported against the size of the population that has been exposed and the extent of the exposure that has occurred in that population. There needs to be a significant number of cases of asthma induced by a particular substance in relation to the total number of people exposed to it, before classification becomes appropriate. Thus, the conclusion could be that a high-production-volume chemical, used in large quantities in many workplaces throughout the world, would not warrant the R42 phrase if only a few cases of asthma associated with its use have been reported over the years. In contrast, 3 cases of asthma among a workforce of 20 in contact with a speciality chemical could well result in the conclusion that the substance warrants classification as a sensitiser. This sort of “clustering” of cases can provide strong evidence with respect to a particular substance, although the case reports would still need careful critical appraisal, and the possibility of shared exposure with another, unsuspected substance should also be considered. Regarding extent of exposure, if a substance is stringently controlled, perhaps due to concern for another toxicological endpoint such as carcinogenicity, it is likely that fewer cases of asthma will become apparent than for a substance of equivalent asthmagenic potential for which historically there has been no such concern and exposure has not been so well controlled. Thus this sort of consideration may also need to be taken into account when making the overall assessment.

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SECTION C: The following substances were considered to meet the new EU criteria, revised in 1996, for classification as a respiratory sensitiser (a cause of asthma) and labelling with R42

C1: AZODICARBONAMIDE

SUMMARY AND CONCLUSION

The results of worker surveys and investigations of individuals show that occupational asthma develops in a substantial proportion of workers exposed to azodicarbonamide. The mechanism underlying the induction of asthma remains to be determined, since there is currently no evidence that an immunological or an irritant reaction is involved.

There is sufficient evidence to conclude that azodicarbonamide meets the revised EU criteria (1996) for classification as a respiratory sensitiser (a cause of asthma) and labelling with R42.

INTRODUCTION

Azodicarbonamide is primarily used as a blowing agent in the rubber and plastics industries. It is used in the expansion of a wide range of polymers including PVC, polyolefins and natural and synthetic rubbers. In the past, azodicarbonamide was also used as a flour improver in the bakery industry, but this practice appears to have been discontinued. It is estimated that several thousand persons are exposed to azodicarbonamide in the workplace. Of this total, it is estimated that only a few hundred persons are exposed as part of their main work activity (i.e. those involved in compounding, mixing or raw material handling).

The following information has been summarised from an HSE Criteria Document for an occupational exposure limit, where a more detailed critical appraisal of the available data can be found (Ball *et al*., 1996).

EVIDENCE FOR WORK-RELATED ASTHMA

There are case reports of individuals suffering asthmatic symptoms linked with azodicarbonamide exposure, but few studies are available in which workers have been challenged with azodicarbonamide. Positive results were obtained in 4 people, after apparently open challenge (Malo *et al*., 1985; Normand *et al*., 1989). The use of an appropriate control suggested that a non-irritant concentration was used in at least 2 of these cases. Another challenge test was negative (Valentino and Comai, 1985).

A workplace health evaluation of 151 workers with current or previous exposure to azodicarbonamide revealed a prevalence of asthmatic symptoms of 18.5% (Slovak, 1981). Of the current workers diagnosed as sensitised, over half developed symptoms within 3 months of first exposure, and 75% within one year. Almost half of those affected reported worsening of symptoms upon repeated exposure and a shortening of the time between returning to work and reappearance of symptoms. Neither symptomatic nor asymptomatic workers showed lung function changes over a shift.

Other studies have reported respiratory complaints in a high proportion of workers (at least 60%) though they have also failed to demonstrate lung function changes over a shift (Ahrenholz and Anderson 1985; Ahrenholz *et al*., 1985). However, other investigators have found such functional changes (Ferris *et al*., 1977).

In the UK between 1989 and 1993, a total of 29 cases of occupational asthma attributed to azodicarbonamide exposure were reported to the SWORD database (figures for 1992 and 1993 indicate that around 6 cases per year are reported).

SUPPORTING DATA

There is currently no evidence that azodicarbonamide causes occupational asthma by an immunological mechanism; skin prick tests have been negative and antibody studies have not been carried out.

Although there are no internationally validated predictive methods for assessing respiratory hypersensitivity, a study using unconjugated azodicarbonamide has been performed in guinea pigs; it was negative (Gerlach *et al*., 1989).

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C2: CARMINE

SUMMARY AND CONCLUSION

Carmine, which is an insect-derived dyestuff, causes occupational asthma in some exposed workers, and a total of 10 positive bronchial challenge test results are available. The mechanism appears to be immunological, and there is evidence that the allergen is not the dye molecule carminic acid, but a high molecular weight component of the preparation.

There is sufficient evidence to conclude that carmine meets the revised EU criteria (1996) for classification as a respiratory sensitiser (a cause of asthma) and labelling with R42.

INTRODUCTION

Carmine is prepared by aqueous extraction and precipitation of cochineal, which is derived from the dried bodies of the female insect *Dactylopius coccus*, also called Coccus cactus. The water-soluble carmine contains about 50% carminic acid, which is an anthraquinone-based dye; the other components are insect-derived materials. Carmine is used for cosmetic, pharmaceutical and histological dyeing, and like cochineal is used as a food colouring and in “Campari” (Burge *et al*., 1979; Quirce *et al*., 1994).

EVIDENCE FOR WORK-RELATED ASTHMA

Reports of occupational asthma associated with the use of carmine are rare, although two groups each found one affected worker in workforces of approximately 50 (Burge *et al*., 1979; Rodriguez *et al*., 1990).

One male patient who was occupationally exposed to carmine had suspected occupational asthma, and airways that proved moderately hyper-reactive to histamine (Durham *et al*., 1987). He underwent bronchial challenge, which was performed single-blind, with either lactose powder coloured with amaranth (control) or 0.1 and 0.3% carmine in lactose. The higher concentration of carmine induced a positive dual response, the lower concentration a borderline response, while the control failed to cause a reaction.

A study was carried out on 9 current and 1 former worker in a natural dye factory which produced carmine and other dyes; conditions were reported to be highly dusty and workers wore face masks (Quirce *et al*., 1994). The total workforce was not stated. Two (1 current, 1 former) workers had work-related asthma, and another had rhinitis. The current worker with asthma, who had hyper-reactive airways, underwent specific bronchial challenge with aerosolised saline or solutions of carminic acid, carmine, cochineal and annatto (also produced at the factory). Three previously unexposed asthmatic controls were also exposed to cochineal and carmine. The subject gave immediate responses to carmine and cochineal, but failed to react to carminic acid or annato, indicating that he was specifically reacting to a component of carmine/cochineal that was not carminic acid. This conclusion was supported by immunological data (see below). None of the controls reacted.

A total of 8 people with carmine-associated occupational asthma have undergone apparently open specific bronchial challenge with carmine powder or solution, with or without control substances (Burge *et al*., 1979; Lenz *et al*., 1983; Tenabene *et al*., 1987; Rodriguez *et al*., 1990). All gave positive results. Latent period to development of asthma varied from 2 months to 10 years.

SUPPORTING DATA

Approximately half the people with carmine related asthma had specific immunoglobulin E (IgE) to carmine, compared to none of the exposed, non-asthmatic workers (Burge *et al*., 1979;

Tenabene *et al*., 1987; Quirce *et al*., 1994). A similar pattern was seen with skin prick or scratch tests. Most workers with asthma had raised total IgE, while most of those without did not (Burge *et al*., 1979; Lenz *et al*., 1983; Tenabene *et al*., 1987; Rodriguez *et al*., 1990; Quirce *et al*., 1994). In contrast to the specific IgE results, specific IgG has been found to carmine in all exposed workers, whether or not they had asthmatic symptoms (Quirce *et al*., 1994). In the same study, the authors demonstrated reactivity in skin prick and radioallergosorbent (RAST) tests in respectively 2 and 1 asthmatic patients. This reactivity was found against carmine and cochineal but not carminic acid or carminic acid bound to human serum albumin. A RAST inhibition test indicated that the reaction involved a 10 - 30 kdalton fraction of carmine.

Anaphylactic or systemic reactions to drinking Campari or carmine solution have occasionally been reported, and have included asthma-like symptoms; one of the patients was RAST and skin prick positive to carmine (Burge *et al*., 1979; Kagi *et al*., 1994).

Carmine has also been reported to cause an allergic alveolitis characterised by cough, dyspnoea and fever (e.g. Christiansen *et al*., 1981).

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C3: CASTOR BEAN DUST

SUMMARY AND CONCLUSION

Several published papers indicate that castor beans have caused occupational asthma in a substantial number of exposed individuals. In a few cases confirmation has come from bronchial challenge tests, although methodological details have not been fully described for these studies. A number of reports have demonstrated positive skin prick tests to castor beans and the presence of specific immunoglobulin E (IgE), suggesting an immunological mechanism. The results of these tests show an apparent association with allergic symptoms in exposed individuals.

There is sufficient evidence to conclude that castor bean dust meets the revised EU criteria (1996) for classification as a respiratory sensitiser (a cause of asthma) and labelling with R42.

INTRODUCTION

The castor bean is the seed of the castor oil or castor bean plant, *Ricinus communis*. Castor bean seeds produce oil and pomace. Castor oil has been used in the production of paint, varnish, plasticisers and dibasic acids and as a component of cosmetics, hair oils, fungistatic preparations, printing inks, nylon, plastics, hydraulic fluids and textile finishing materials. Pomace is used as fertiliser. Allergy to castor beans has occurred among people living in the vicinity of processing plants (Mendes, 1980). Some of the reports documented below describe observations of castor bean allergy derived from industries where the beans are not subjected to primary processing but may be a contaminant of other materials.

EVIDENCE FOR WORK-RELATED ASTHMA

Davison *et al* (1983), investigated asthma in 3 merchant seamen and 2 laboratory workers exposed to castor beans. The seamen all became wheezy approximately 1 hour after the hold of their ship, containing castor beans and other materials, was opened for unloading. Their symptoms continued until they were admitted to hospital. Recovery was rapid following treatment with bronchodilators and corticosteroids. The laboratory personnel experienced wheezing and chest tightness, apparently related to the preparation of castor bean extract. Bronchial challenge was performed on the seamen using what was described as ‘standard techniques’. Specific methodological details were not given. Measurements of the forced expiratory volume in one second (FEV_1) were stable prior to the test. One subject developed a 49% reduction in FEV_1 after 9.5 hours, and the second a reduction of 40% at 11.5 hours. The third patient did not show a significant fall in FEV_1. The positive findings are consistent with a late asthmatic reaction to castor beans. All 5 subjects tested positive for specific IgE antibodies.

Merget *et al* (1994) described the case of an agricultural products merchant with occupational asthma and rhinitis. The subject was exposed during the course of his work to a variety of materials, including castor bean fertiliser. Bronchial challenge tests were conducted using fertiliser extract and methacholine, and controlled by administration of placebo. Specific airway resistance was recorded with a volume constant body plethysmograph. Inhalation of fertiliser extract solution showed a clear immediate asthmatic response with slow recovery, while the findings for methacholine indicated severe bronchial hyperresponsiveness. The subject also proved positive in a skin prick test using a solution of the fertiliser, and demonstrated IgE against castor bean extract.

SUPPORTING DATA

Kemeny *et al* (1981) measured total IgE and castor bean specific IgE in 39 dock workers in Port Sudan exposed to castor bean dust and with symptoms of rhinitis and/or asthma, 12

asymptomatic dock workers exposed to the dust, 43 residents of Port Sudan who received no direct exposure and 36 non-allergic subjects from the UK. The highest levels of total IgE were observed in the group of symptomatic workers (902 IU/ml). All groups from Port Sudan had greater levels of total IgE when compared with UK subjects. A positive result for castor bean specific IgE was found in up to 100% of symptomatic workers, 16% of asymptomatic workers, 35% of residents and 0% of those from the UK. The levels observed in the first group were often very high. All symptomatic workers also showed a positive skin prick test with a high dilution of castor bean extract.

In a study of 50 selected workers from coffee processing plants, 18/25 with respiratory, eye, nose or skin symptoms, and 1/25 without symptoms demonstrated specific IgE to castor beans (Osterman *et al*., 1982). In the same report 19/129 coffee processing workers with respiratory, eye, nose or skin symptoms and 3/129 workers without such symptoms demonstrated a positive skin prick test with castor bean extract. It was presumed that castor beans contaminated the sacks before they were reused for coffee beans.

Castor bean allergy has been investigated in 16 dock workers handling sacks of green coffee who developed symptoms of either rhinitis or asthma at work (Patussi *et al*., 1990). A positive skin prick test with castor bean extract was found in 15/16 and the skin prick positive subjects also had specific IgE.

Topping *et al* (1982) investigated castor bean allergy among 26 workers in a felt manufacturing plant. Twelve had symptoms of rhinitis and conjunctivitis and 7 complained of wheezing. Specific IgE antibodies were detected in 15/23 subjects, including 12/12 with symptoms. A skin prick test with castor bean extract was positive in 12/20 subjects, including 10/11 with symptoms. It was found that one of the raw materials for the felt was old sacking that had previously been used for castor beans.

Thorpe *et al* (1987) studied a group of 96 people (dock workers and residents) in Marseilles who had consulted their doctor complaining of allergic symptoms of asthma and rhinitis and had a positive skin test to castor bean extract. Total IgE levels were higher in this group (174 IU/ml) than among a control group of 111 blood donors from the Marseilles region. In the test group, 90% had specific IgE compared with 0% of controls. Often the specific IgE levels were very high.

Specific IgE to castor bean extract was identified in 22/150 coffee workers (Thomas *et al*., 1991). Nineteen subjects in the same group demonstrated work related respiratory symptoms.

In a survey of 256 workers exposed to castor beans, 57% were positive in a skin prick test with castor bean extract, compared with 0% of 77 controls (Fakhri and Erwa, 1988).

In a group of 211 employees at a coffee manufacturing plant, 27 % showed symptoms of rhinitis and/or asthma. A skin prick test to castor bean extract was positive in 22% (Romano *et al*., 1995).

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C4: CHLORAMINE-T

SUMMARY AND CONCLUSION

A number of reports indicate that workers who have been exposed to chloramine-T (sodium N-chloro-4-toluenesulphonamide) have developed asthma. Although the available bronchial challenge data have not been generated under the most stringent conditions, overall they do provide reasonable evidence that the asthma apparent in these workers was indeed induced by chloramine-T. There is evidence for an immune response occurring in those people with symptoms, specific IgE and skin prick tests showing a correlation with bronchial challenge data.

There is sufficient evidence to conclude that chloramine-T meets the revised EU criteria (1996) for classification as a respiratory sensitiser (a cause of asthma) and labelling with R42.

INTRODUCTION

Chloramine-T is highly reactive with proteins, creating an antigenic determinant formed by the p-toluenesulphonyl group. It is used as a disinfectant in a range of applications because of its antiviral, bactericidal and fungicidal properties. It seems to act by the liberation of hypochlorous acid which decomposes to chloride ions and oxygen, the latter being the disinfecting agent. Chloramine-T dust has been reported to be irritating to the respiratory tract, although primary data to substantiate this have not been identified (Evans *et al*., 1986; Wass *et al*., 1989; Blomqvist *et al*., 1991).

EVIDENCE FOR WORK-RELATED ASTHMA

There are several reports indicating that workers who have been exposed to chloramine-T may develop work-related asthma. In many of these studies, people with nasal and/or respiratory symptoms, associated with working with chloramine-T, have undergone bronchial challenge. Although none of the challenges have been blinded, some studies have involved determining non-irritant conditions by challenging either normal or asthmatic controls. However, exposure concentrations have not been measured. In addition to the above studies, there are several reports available in which exposure-related symptoms have been noted in workers, but specific bronchial challenges have not been performed.

Five workers who had been exposed occupationally to chloramine-T had all developed nasal irritation and/or respiratory symptoms either at work or nocturnally, with a latent period of 2 to 8 months after first exposure (Dijkman *et al*., 1981; Kramps *et al*., 1981). All underwent unblinded bronchial challenge with nebulised chloramine-T solution or saline and gave positive reactions (2 early, 2 late, 1 dual) to chloramine-T but not saline, while 2 unexposed controls (one atopic) failed to react. None of the workers had a previous history of asthma, although 3 of the 4 tested gave positive skin prick tests to common allergens.

A man presented with a six-year history of work-related rhinoconjunctivitis and asthma which had begun four years after first using chloramine-T (Blasco *et al*., 1992). He had not suffered a “massive” exposure to the substance. Colleagues similarly exposed had no clinical complaints. Unblinded bronchial challenge testing with either saline or nebulised chloramine-T solution induced a dual response with the latter. The same challenge conditions for two previously unexposed, atopic asthma patients failed to elicit a response. The worker was not atopic.

Brief details were given of 9 people who developed rhinitis and/or asthma associated with occupational exposure to chloramine-T (Schoeneich and Wallenstein 1985). All had experienced a latent period (“a few exposures” to 3 years) before developing symptoms, which occurred during the mixing of chloramine-T powder in water. The results of bronchial challenges were positive for 4 of the 5 subjects tested, and consisted of 2 immediate and 2 late responses; previously unexposed controls failed to react. Two other subjects were challenged nasally, and

one gave an immediate response. Although none had a history of atopy, two of the nine gave positive skin prick tests to common allergens, only one of whom reacted to chloramine-T at bronchial challenge.

One worker who had bronchial asthma associated with exposure to chloramine-T reacted positively to bronchial challenge under conditions reported to be non-irritating to asthmatic controls not previously exposed to the substance (Popa *et al*., 1969). In this brief report, no previous history was given, but the person was atopic (positive skin prick test to common allergens).

There are four reports in which single cases of people with occupational asthma have undergone bronchial challenge with chloramine-T as either a powder or in aqueous solution, but without any controls: all gave a positive reaction (Charles 1979; Dellabianca *et al*., 1988; Romeo *et al*., 1988; Blomqvist *et al*., 1991). One woman developed an anaphylactic reaction following a strong immediate response (Blomqvist *et al*., 1991). A positive nasal challenge occurred in a further worker; the same study reported a case in which bronchial challenge was inconclusive (Jouannique *et al*., 1992). Only one of these people was atopic.

Other cases of asthma or rhinitis associated with exposure to chloramine-T, but unsubstantiated by bronchial or nasal challenge, have been reported (Bourne *et al*., 1979; Beck, 1983; Dooms-Goossens *et al*., 1983; Wass *et al*., 1989; Blomqvist *et al*., 1991). Two of the men were reported to have developed their symptoms after a high accidental exposure (Bourne *et al*., 1979).

SUPPORTING DATA

The immunological responses to chloramine-T in exposed people have been studied extensively (Popa *et al*., 1969; Bourne *et al*., 1979; Dijkman *et al*., 1981; Kramps *et al*., 1981; Beck, 1983; Dooms-Goossens *et al*., 1983; Schoeneich and Wallenstein, 1985; Dellabianca *et al*., 1988; Romeo *et al*., 1988; Blomqvist *et al*., 1989; Wass *et al*., 1989; Blasco *et al*., 1992; Jouannique *et al*., 1992).

Total serum immunoglobulin E (IgE) levels have generally been found to be normal in those exposed to chloramine-T. The presence of specific IgE to chloramine-T-human serum albumin (CT-HSA) conjugates, measured by radioallergosorbent test, has been found in most exposed, symptomatic people. Although no comprehensive studies have been conducted, there are indications that asymptomatic, exposed workers do not have specific IgE to CT-HSA in their sera. The studies which allow a comparison of bronchial or nasal challenge results and specific IgE suggest a positive correlation between the two. Skin prick tests with free or HSA-conjugated chloramine-T have also shown a relationship between a positive result and the presence of symptoms or positive challenge data. Other occasionally performed immunological tests (histamine release, Prausnitz-Kustner transfer reaction) have shown a similar correlation.

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C5: CHLOROPLATINATES AND OTHER HALOGENOPLATINATES

SUMMARY AND CONCLUSION

There is a large body of evidence from occupational studies (including bronchial challenge data) and individual case-reports for the induction of asthma by chloroplatinate salts. The results of total immunoglobulin E (IgE) and radioallergosorbent tests (RAST) appear to indicate that these responses are immunologically mediated. Although no useful information is available for other halogenoplatinates, structure activity considerations indicate that asthmagenic potential would also be likely for these substances.

There is sufficient evidence to conclude that chloroplatinates and other halogenoplatinates meet the revised EU criteria (1996) for classification as respiratory sensitisers (causes of asthma) and labelling with R42.

INTRODUCTION

The main platinum salts of industrial relevance are those produced during the refining of platinum metal, namely ammonium, sodium and potassium tetrachloroplatinates and hexachloroplatinates. Workers may be exposed either to aqueous aerosols or to the dry dust of these salts. Workers may also be exposed to chloroplatinates in the manufacture of platinum catalysts and electrodes. It is thought that industrial exposure to halogenoplatinate compounds other than the chloroplatinates is negligible.

The following information has been summarised from an HSE Criteria Document for an Occupational Exposure Limit, where a more detailed appraisal of the evidence can be found (Meldrum *et al*., 1996).

EVIDENCE FOR WORK-RELATED ASTHMA

Numerous occupational studies from as early as 1945 (e.g. Hunter *et al*., 1945) provide evidence for the induction of allergic skin and respiratory responses in platinum refinery workers exposed to chloroplatinate salts. Similar findings have been reported in workers exposed to chloroplatinates when making platinum electrodes (Shima *et al*., 1984). In general, reported prevalences of skin and respiratory symptoms among the various cohorts investigated have been in the region of 40-60%. Reported latency periods from the first contact with platinum salts to the onset of symptoms range from a few months to 6 years. Positive bronchial challenge test results with chloroplatinic acid were obtained in the majority of former workers from platinum refineries who had work-related symptoms of asthma, rhinitis and conjunctivitis (Merget *et al*., 1991). Testing was carried out 15 months after exposure. In contrast, no positive responses could be elicited in control subjects with episodic asthma but no prior exposure to chloroplatinates.

In a study of current and former workers at a platinum refinery in the USA (Baker *et al*., 1990), immunological investigations showed raised IgE levels in 23% of current and 52% of former workers (the latter had ceased employment due to suspected allergy to platinum salts). Positive RAST scores were obtained in 20 of 22 workers with positive skin tests to ammonium or sodium hexachloroplatinate, compared with only 8 of 94 workers with negative skin tests. A questionnaire revealed rhinitis in 44% of current workers and 10% of former workers, and asthma (defined as wheezing and at least one other respiratory symptom such as cough, breathlessness or chest tightness) in 29% and 52% of current and former workers respectively. Lung function testing showed airways obstruction in 6% of current and 18% of former workers. Positive cold air challenge reactions occurred in 11% of current and 30% of former workers. Repeat investigations carried out 12 months later confirmed these results.

In addition, numerous case reports indicate the development of allergic responses, including cough, dyspnoea, chest tightness, rhinorhoea and eye irritation, following exposure to

chloroplatinate salts (e.g. Freedman and Krupey, 1968; Schultze-Werninghaus *et al*., 1978; Orbaek, 1982). In some of these cases, skin testing with solutions of chloroplatinate salts provoked anaphylactic shock.

No documented evidence is available regarding the ability of halogenoplatinates other than chloroplatinates to induce asthma. It is, however, likely that this is a reflection of the lack of significant exposure, and structural-activity considerations indicate that asthmagenic potential would also be likely for these substances.

SUPPORTING DATA

Immunological investigations as well as skin prick tests were carried out on 306 non-atopic platinum refinery workers (Murdoch and Pepys, 1987). The findings included raised levels of total IgE and positive RAST results for platinum salt antibody in those with positive skin prick responses to platinum salts.

In another study, higher IgE levels were noted among platinum refinery workers with work-related symptoms (coughing, rhinitis, dyspnoea or conjunctivitis) compared with workers without symptoms (Bolm-Audorff *et al*., 1990).

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C6: CHROMIUM (VI) COMPOUNDS

SUMMARY AND CONCLUSION

A good number of studies provide evidence that inhaled hexavalent chromium can cause asthma, and there are positive findings from several well-conducted bronchial challenge tests. The mechanism by which chromium causes asthma is not well-defined, but there is currently little evidence of immunological effects.

There is sufficient evidence to conclude that hexavalent chromium compounds meet the revised EU criteria (1996) for classification as respiratory sensitisers (causes of asthma) and labelling with R42.

INTRODUCTION

Inorganic chromium exists as the elemental metal and in a range of oxidation states, for which information is primarily available on 3, Cr (III) and 6, Cr (VI). Both the oxidation state and the water solubility (which can vary widely according to the compound) affect the biological activity. In general, hexavalent chromium is far more toxicologically active than trivalent chromium. Highly water-soluble hexavalent chromium is very irritant to the respiratory tract, inducing inflammatory changes with necrosis or ulceration. Stainless steel welding fumes contain a heterogeneous chromium component and also nickel (Fairhurst and Minty, 1989).

EVIDENCE FOR WORK-RELATED ASTHMA

The early literature contains reports of small numbers of workers suffering occupational asthma associated with the use of hexavalent and possibly trivalent chromium (Joules, 1932; Card, 1935; Broch, 1949; Tolot *et al*., 1956; Marechal, 1957; Williams, 1969). In more recent studies, bronchial challenge tests have been carried out and sometimes the use of unexposed control subjects has been included.

A recent report describes 6 electroplating workers who were identified at a specialist lung clinic as suffering from occupational asthma induced by chromium (Bright *et al*., 1997). The latent periods for development of the asthma were in the range 8 months to 6 years. Single-blinded bronchial challenge testing with potassium dichromate confirmed the diagnosis in each case, with 2 early, one late and 3 dual responses. Saline was used as the negative control. Serial peak expiratory flow records were obtained for 4 of the subjects during and away from exposure, and these indicated a significant work-related effect. Overall, this well-conducted study provides good evidence that chromium can induce asthma.

Another report describes a welder who was exposed to chromium (VI) trioxide vapours for 10 years before developing dyspnoea and an urticarial rash following an incident involving particularly prolonged exposure (Moller *et al*., 1986). He underwent single-blinded bronchial challenge with nebulised sodium chromate, Cr(VI), and gave a late reaction accompanied by an urticarial rash. Saline was used for the control challenge. Two workers, one of whom had hyperresponsive airways, had previously failed to react to challenge with the same concentrations of chromate.

An electroplater who had a brief history of work-related asthma was examined by double-blind challenge with fumes from chromium (III) sulphate and a placebo solution (Novey *et al*., 1983). He gave an immediate reaction with the chromium fumes only, whereas 2 ‘allergic’ asthma patients similarly exposed did not react. In another study, 4 subjects had a history of occupational asthma associated with the use of chromium (probably hexavalent), which developed after latent periods of 3 months to 9 years (Park *et al*., 1994). Two also had rhinitis and one urticaria. Bronchial challenge tests (apparently unblinded) were performed with saline and nebulised dichromate solution on different days. All 4 gave positive challenge reactions (one early and three

dual) with the hexavalent chromium solution only. Two patients with intrinsic asthma and 2 normal controls failed to react to the same concentrations. Similarly, the non-irritant concentration of potassium dichromate to be used at bronchial challenge was determined in 6 asthmatic subjects, giving no reactions, before testing 2 people who had chromium-related asthma (Popa *et al*., 1969). Both reacted at challenge (one early, one late response).

Other studies, some superficially reported, are available in which control solutions have been used or people previously unexposed to chromium have also been challenged (Keskinen *et al*., 1980; Cirla *et al*., 1982; Dahl *et al*., 1982; Saakadze *et al*., 1984; Olaguibel and Basomba, 1989). These to non-irritant concentrations of hexavalent chromium. Three of the studies were carried out in welders who reacted to stainless steel, but not mild steel, welding fumes (Keskinen *et al*., 1980; Cirla *et al*., 1982; Dahl *et al*., 1982).

SUPPORTING DATA

Immunological studies have been carried out in workers who have developed occupational asthma after being exposed to chromium, but none are available for exposed workers who have remained healthy. Specific immunoglobulin E (IgE) has been measured (by radioallergosorbent test) in only 2 subjects, one of whom was negative to hexavalent chromium and one positive to the trivalent form; in both of them immediate skin prick or intradermal reactions were absent (Novey *et al*., 1983; Moller *et al*., 1986). Immediate skin reactions (scratch, prick or intradermal) to hexavalent chromium in people with chromium-associated occupational asthma have more often been negative (11 people) than positive (5 people). In addition, Prausnitz-Kustner passive transfer (skin) tests were negative in 2 workers (Joules, 1932; Card, 1935; Popa *et al*., 1969; Cirla *et al*., 1982; Dahl *et al*., 1982; Novey *et al*., 1983; Moller *et al*., 1986; Olaguibel and Basomba, 1989; Park *et al*., 1994). However, asthmatic attacks were induced in three people tested intradermally (known to have been performed blinded in at least 2 cases), one of whom failed to react to the skin test (Joules, 1932; Card, 1935; Popa *et al*., 1969).

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C7: COBALT (METAL AND COMPOUNDS)

SUMMARY AND CONCLUSION

Limited epidemiological findings supported by numerous case reports indicate that cobalt can cause asthma in humans following exposure at work, in industries such as hard metal production and diamond polishing. The process underlying cobalt-induced asthma appears to have an immunological component, although other mechanisms such as irritancy may also operate.

There is sufficient evidence to conclude that cobalt (metal and compounds) meets the revised EU criteria (1996) for classification as a respiratory sensitiser (a cause of asthma) and labelling with R42.

INTRODUCTION

Cobalt-containing atmospheres are generated in several industries, including hard metal manufacture and use, diamond polishing and production of the metal from ore. Repeated exposure of workers in these industries has resulted in two forms of lung disease - diffuse interstitial pulmonary fibrosis and asthma. Cobalt (as the metal dust or as solubilised ionic cobalt) is generally considered to be the causative agent for both of these conditions, although the atmospheres generated also contain tungsten and other metal carbides (hard metal industries) or amorphous carbon, diamond and iron (diamond polishing).

The following information has been summarised from an HSE Toxicity Review, where a more detailed critical appraisal of the available data can be found (Evans *et al*., 1993).

EVIDENCE FOR WORK-RELATED ASTHMA

Most of the information relating to cobalt-induced asthma is in the form of case reports. The first cases were noted more than 30 years ago (Key, 1961). Since then, numerous individual cases occurring in workers engaged in hard metal manufacture or use have been documented (e.g. Sjogren *et al*., 1980; Davison *et al*., 1983; Pisati *et al*., 1986). There is also a study in a Japanese factory identifying 18 cases of asthma related to hard metal exposure, a prevalence of 5.6% (Kusaka *et al*., 1986), and 15 cases were reported in a Finnish works producing cobalt metal from ores (Roto, 1980). Another report described 3 cases of asthma in Belgian diamond polishers (Gheysens *et al*., 1985). In some of these studies bronchial challenge with hard metal dust, cobalt metal powder or ionic cobalt aerosol was performed, and the positive results obtained confirm the role of hard metal and diamond polishing dusts (and their cobalt component) in the production of asthma.

SUPPORTING DATA

The mechanism for the asthma that occurs in workers in the hard metal and diamond polishing industries appears to have an immunological component. In a study of Japanese hard metal workers with asthma and positive bronchial challenge responses to cobalt chloride, the sera from 6 out of 12 subjects gave positive responses in a radioallergosorbent test for specific immunoglobulin E antibodies to cobalt-human serum albumin conjugate (Shirakawa *et al*., 1988). In most studies, however, the presence of specific antibodies to cobalt has not been investigated.

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C8: COW EPITHELIUM/URINE

SUMMARY AND CONCLUSION

Several reports indicate that exposure to cow epithelium/urine can cause occupational asthma, although details of occupational exposure and symptomatology in these studies are sparse. Additionally, where challenge tests or lung function tests have been used to confirm the diagnosis, the procedures are poorly described. Positive findings from assays of specific immunoglobulin (Ig) and skin prick tests provide evidence of an immunological response.

There is sufficient evidence to conclude that cow epithelium/urine meets the revised EU criteria (1996) for classification as a respiratory sensitiser (a cause of asthma) and labelling with R42.

INTRODUCTION

Information on cow epithelium/urine as a cause of occupational asthma has been largely gathered from studies carried out in either Finland or Denmark. The combined term epithelium/urine may be applied to the studies outlined below which have reported on reactions to cow dander, hair or antigen purified from epithelium and urine.

EVIDENCE FOR WORK-RELATED ASTHMA

Several reports have described a group of up to 17 patients with asthma resulting from exposure to cow dander or to cows *per se* (Prahl *et al*., 1981; Prahl and Nexo, 1982; Prahl *et al*., 1982). The diagnosis was based on anamnesis and the findings of bronchial challenge, radioallergosorbent (RAST) and skin prick tests. A complete account of occupations, symptomatology and the challenge tests was not given.

In a study of 41 dairy farmers exposed to bovine dust, Virtanen *et al* (1988) diagnosed 9 cases of rhinitis and 4 cases of asthma, both of bovine origin, based on completed questionnaires from 33 respondents. The age of farmers, used as an indicator of duration of exposure to bovine materials, did not correlate with either rhinitis or asthma.

Ylonen *et al* (1992a, 1992b) have described a group of 49 dairy farmers with clinically diagnosed asthma of bovine origin. The diagnosis was confirmed, in part, by a challenge test using cow epithelial antigen, which required demonstration of a 20% reduction in peak expiratory flow or forced expiratory flow in one second to be considered positive. Further details of this test were not provided.

SUPPORTING DATA

IgG antibodies specific for cow hair and dander have been detected in some patients with bovine dander induced asthma (Prahl *et al*., 1981). In a similar group of patients, specific IgE was detected in 8/8 subjects (Prahl and Nexo, 1982). Both IgG and IgE antibodies to bovine epithelium and urine have been found among 41 dairy farmers studied by Virtanen *et al* (1988). Antibody titres were not associated with allergic symptoms. Ylonen *et al* (1992a), found the level of IgE to cow epithelium among 49 dairy farmers with asthma of bovine origin, was statistically significantly higher when compared with levels in non-asthmatic farmers or students. A study of 19 dairy farmers with nasal symptoms associated with working in cowhouses, revealed 7 subjects with a positive RAST result for cow dander (Rautiainen *et al*., 1992).

Positive skin prick tests to cow dander and hair have been reported in 10/10 patients with cow induced asthma (Prahl *et al*., 1982) and in 12/19 dairy farmers with nasal symptoms related to working with cows (Rautiainen *et al*., 1992). Mean skin test wheal area (adjusted for age, sex, atopic status) following skin exposure to cow dander was statistically significantly greater in a group of 121 dairy farmers with allergic rhinitis and or asthma when compared with 64

asymptomatic dairy farmers (Terho *et al*., 1987). In a study of 742 agricultural workers, 3.8% produced a positive skin response to cow hair (Maria *et al*., 1991).

Nasal challenge with cow dander in 50 dairy farmers with rhinitis produced a positive reaction in 10 cases compared with 0/20 asymptomatic dairy farmers (Terho *et al*., 1985). Nasal challenge in 19 dairy farmers with nasal symptoms associated with exposure to cows showed a positive response in up to 7 cases when bovine epithelium was used and 6 cases when bovine urine was used as the test material (Rautiainen *et al*., 1992).

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C9: CRUSTACEAN PROTEINS

SUMMARY AND CONCLUSION

Several reports indicate that exposure to crustacean protein in the workplace can lead to the development of occupational asthma. This occurs in a substantial proportion of the workforce when exposure is to prawn or crab. These findings are supported by data from adequately conducted bronchial challenge and lung function tests. The results of assays for immunoglobulin E (IgE) to crustacean protein and skin prick tests have demonstrated an immunological response in many workers with respiratory symptoms.

There is sufficient evidence to conclude that crustacean protein meets the revised EU criteria (1996) for classification as a respiratory sensitiser (a cause of asthma) and labelling with R42.

INTRODUCTION

Crustacea belong to the phylum Arthropoda and include prawn, shrimp, crab and lobster. Information relevant to occupational asthma has been located for all of these species.

EVIDENCE FOR WORK-RELATED ASTHMA

In a study of a prawn processing factory, respiratory symptoms (commonly wheeze, cough and breathlessness) developed in 18 out of 50 exposed workers 6 weeks after the introduction of an 'air blowing' procedure to remove meat from prawns (Gaddie *et al*., 1980). Symptoms appeared between 0.5 - 6 hours after starting work, often persisting into the evening, but disappeared at weekends and during holidays. Reduction of vital capacity was noted in 12/18 symptomatic subjects and, when symptoms were present, there was a reduction of the forced expiratory volume in one second (FEV_1) below 70% of the vital capacity. Two affected workers underwent bronchial challenge with various concentrations of prawn protein in saline. At the maximum exposure level, the first worker developed dyspnoea, cough and wheeze after 3 minutes inhalation. The FEV_1 and forced vital capacity (FVC) dropped rapidly. Recovery occurred after 2 hours. The second subject developed wheeze and dyspnoea after 5 minutes inhalation. After 2 hours, breathlessness, an unproductive cough, myalgia and fever occurred. There was a sharp fall in FEV_1 and FVC, with a maximum reduction at 6-8 hours. No changes were observed after inhalation of saline alone, or after inhalation of prawn protein by 2 healthy volunteers. The results from these challenge tests provide evidence that prawn protein can induce occupational asthma. Symptoms in all but 3 workers disappeared when the process by which meat was removed from the prawns was changed.

A worker involved in cooking prawns developed conjunctival irritation, cough and dyspnoea after 5 years (Dugue *et al*., 1988). The symptoms disappeared following cessation of employment. When bronchial challenge was conducted in a single-blinded manner, FEV_1 fell by 30-39% following challenge with 'prawn broth'. A lower concentration of prawn broth failed to induce any significant change in FEV_1. Non-specific challenge testing with carbamylcholine produced a 22% reduction in FEV_1.

A case of occupational asthma related to exposure to shrimpmeal has been reported by Carino *et al*., 1985). A worker in the aquaculture industry developed cough, shortness of breath and wheezing whilst preparing or handling shrimpmeal. Bronchial challenge with methacholine indicated moderate airways hyperresponsiveness. Bronchial challenge with shrimpmeal produced a dual asthmatic response. Exposure to lactose or chitin elicited no asthmatic response. Two non-asthmatic and 3 atopic asthmatic controls did not give asthmatic reactions with the shrimpmeal.

Workers at two snow crab processing factories have been investigated for evidence of occupational asthma both prior to the fishery season and when back at work (Cartier *et al*., 1984).

In the preseasonal survey, 64 out of 303 participating workers (97% of the total workforce) provided a symptomatic history that was highly suggestive of occupational asthma. Lung function tests in 298 subjects revealed significant airway obstruction in 13, including some with and some without symptoms. In those with a history of occupational asthma, 39/56 demonstrated bronchial hyperresponsiveness on challenge testing with histamine.

Bronchial challenge was carried out in 32/64 workers with a history of occupational asthma and 14 with exacerbation of asthma on return to work. The test was conducted with a boiling water extract of crab or with subjects standing close to boiling pots whilst at work. Control challenge was conducted using saline. Results were positive (sustained fall in FEV_1 >15% when compared with baseline and or control values) in 33 cases. There were 1 immediate, 23 late and 9 dual responses. Two subjects had significant eosinophilia after challenge. Further testing of subjects with asthmatic symptoms on return to work showed a significant fall in FEV_1, compared with preseasonal values, in 18/27. Progressive deterioration in serial peak expiratory flow rate measurements at work with improvement on cessation of exposure was noted in 12/14 with satisfactory recordings. A significant increase in bronchial hyperresponsiveness after return to work was observed in 16 cases and significant eosinophilia was demonstrated in 15/27 subjects. It was concluded that the results of the challenge and lung function tests confirmed occupational asthma in a total of 46 cases. Certainly a significant proportion of the workforce studied developed asthma as a result of exposure to crab.

Respiratory symptoms of 186 workers at 3 king crab processing plants have been compared with those of 36 workers in a fish processing factory (Orford and Wilson, 1985). Pulmonary function, measured prior to and immediately after work, was assessed in 15 subjects from the first and 11 from the second group. Despite having smoked less than fish processors, crab processors had a greater frequency of respiratory symptoms. No significant deficits in lung function were detected in either group. Further analysis of individual data revealed significant impairment of pulmonary function related to work in 2 crab process workers.

In a case study, a chef presented with wheezing, dyspnoea and cough 4 years after starting work involving the preparation of lobster (Patel and Cockcroft, 1990). Spirometry showed reversible airflow obstruction and histamine challenge revealed marked airway hyperresponsiveness. Full details of the methods were not provided. Bronchial challenge showed no response with diluent but, following challenge with lobster extract, the FEV_1 fell by 22% in an immediate asthmatic response.

In a study of 57 workers involved in shrimp and clam production, exposure to shrimps gave rise to rhinoconjunctiuvitis in 3 and asthma in 2 subjects (Desjardins *et al*., 1995). Asthma in one individual was confirmed by a positive challenge reaction to a mixture of shrimp with lactose.

SUPPORTING DATA

In a study of 50 workers exposed to an aerosol of prawns, 7/18 with respiratory symptoms and 1/32 without symptoms demonstrated prawn specific IgE (Gaddie *et al*., 1980). Corresponding figures for a skin prick test using prawn extract were 7/17 and 6/32.

A skin prick test in a worker involved in cooking of prawns was positive with prawn extract and prawn broth as well as crab and crayfish (Dugue *et al*., 1988). Tests with codeine phosphate and solvent were negative.

Levels of serum IgE and IgG antibodies to prawn antigens were measured in 26 workers complaining of respiratory symptoms resulting from working in a prawn processing factory (McSharry *et al*., 1994). All subjects worked in an area where meat was extracted from the prawns by water jets, generating an aerosol. Symptoms appeared 3 years (median) after taking up employment. Each symptomatic worker was matched for age, sex and years of exposure with an asymptomatic control subject working in the same part of the factory. Specific IgE to prawn

antigens was detected in 15 workers with symptoms and in one asymptomatic worker. Specific IgG was found in 18 individuals from each group.

In a study of a single case of occupational asthma related to shrimpmeal exposure, a skin prick test to shrimpmeal was positive and specific IgE to shrimp and crab was identified (Carino *et al*., 1985).

A skin prick test using crab extracts was conducted on 303 workers involved with snow crab processing (Cartier *et al*., 1984). Interpretable skin reactions occurred in 298, 65 of which were positive (27/44 with occupational asthma, 38/254 without). Further study of these workers showed a significant relationship between the presence of immediate skin reactivity or increased serum levels of specific IgE to crab extracts and the occurrence of occupational asthma (Cartier *et al*., 1986).

In a study of 57 workers involved in shrimp and clam production, 9 showed a positive skin prick test to shrimp and 8 showed an increase in specific IgE to shrimp (Desjardins *et al*., 1995).

Intradermal skin tests, using crab antigens, among 15 king crab processors produced a positive response in 9 cases (Orford and Wilson, 1985). Negative responses were observed in a control group of 11 fish processors.

A positive skin prick test to lobster extract has been observed in a case of occupational asthma due to handling of lobster by a chef (Patel and Cockcroft, 1990).

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C10: DIAZONIUM SALTS

SUMMARY AND CONCLUSION

The available data are limited but indicate that diazonium salts are capable of causing occupational asthma. Similarly, mechanistic information is sparse, but it is clear that an immunological response occurs in a proportion of exposed, symptomatic workers.

There is sufficient evidence to conclude that diazonium salts meet the revised EU criteria (1996) for classification as respiratory sensitisers (causes of asthma) and labelling with R42.

INTRODUCTION

Diazonium salts are intermediates used in the manufacture of some reactive dyes, photocopier paper and during fluorine polymer production. It has been reported that most workers exposed to the dust experience respiratory and mucosal irritation (Armeli, 1968; Graham *et al*., 1981; Luczynska *et al*., 1990).

EVIDENCE FOR WORK-RELATED ASTHMA

The available evidence is limited but suggests that the dust of diazonium salts can cause occupational asthma in previously healthy people. In one study, 19 of 45 exposed workers developed asthmatic symptoms, but these were largely unconfirmed cases (Luczynska *et al*., 1990). An earlier report provides 4 case histories (Armeli, 1968). A total of three people have undergone simulated occupational bronchial challenge, using either lactose powder (control) or a low concentration of the diazonium salt in lactose (Graham *et al*., 1981; Luczynska *et al*., 1990). These were apparently unblinded tests, and no previously unexposed control subjects were included. All three reacted to challenge with the diazonium salt but not the lactose, giving 2 late and 1 dual responses. These data confirm that diazonium salts can provoke an asthmatic response but are not sufficient to exclude an irritant mechanism.

SUPPORTING DATA

Specific immunoglobulin E (IgE) to a conjugate of a diazonium salt and human serum albumin was measured in the sera of 45 workers, all of whom were exposed to the salt as a powder (Luczynska *et al*., 1990). Ten workers were asymptomatic and a further ten had “irritant” symptoms of sneezing, sore throat and cough; none of these 20 had increased specific IgE levels. Of the 25 with asthmatic symptoms (wheeze, chest tightness), 9 had increased specific IgE. Two of the 25 had undergone bronchial challenge; one had increased specific IgE, the other did not. In another study, total IgE was raised in one man with diazonium-associated occupational asthma who reacted at bronchial challenge (Graham *et al*., 1981).

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C11: ETHYLENEDIAMINE

SUMMARY AND CONCLUSION

A number of reports indicate that exposure of workers to ethylenediamine (EDA) can produce occupational asthma, and one well-conducted study in particular provides good evidence that it can induce a hypersensitive state in exposed subjects. The mechanism underlying the induction of asthma has not been established, but clearly immunological and/or irritant reactions could plausibly be involved.

There is sufficient evidence to conclude that EDA meets the revised EU criteria (1996) for classification as a respiratory sensitiser (a cause of asthma) and labelling with R42.

INTRODUCTION

Ethylenediamine is used as an intermediate in the manufacture of various industrial chemicals, organic flocculants, urea resins and fatty bisamides. It is also used in the production of formulations for use in the printed circuit board and metal finishing industries, as an accelerator or curing agent in epoxy coatings/resins and in the manufacture of pharmaceuticals. It is classified as corrosive, so that the vapour is likely to be irritating to the respiratory tract, and its potential as a skin sensitiser is well known in animals and humans, in the latter case from its clinical use in aminophylline.

The following information has been summarised from a HSE Risk Assessment Document, where a more detailed critical appraisal of the available data can be found (Brooke *et al*., 1996).

EVIDENCE FOR WORK-RELATED ASTHMA

In a well-conducted study, a series of individuals with asthmatic symptoms were investigated, 6 of whom gave immediate reactions to ethylenediamine in the workplace (Popa *et al*., 1969). None of the subjects had a history of respiratory disorder prior to occupational exposure, and in all cases the asthma was associated only with occupational exposure. Four of the 6 showed immediate asthmatic responses following bronchial challenge testing with sub-irritant concentrations of ethylenediamine vapour, giving marked reductions in forced expiratory volume in one second (FEV_1) compared with controls. Bronchial challenges with common allergens were negative. In the two other subjects, bronchial challenge tests with ethylenediamine and common allergens were negative.

A number of other, less informative studies are available. Lam and Chan-Yeung (1980) and Chan-Yeung (1982) describe the case of a worker in a photographic laboratory who had no previous history of asthma and who developed work-related asthma after 2.5 years of exposure to a variety of chemicals, including ethylenediamine. In a bronchial challenge test, exposure to an unknown concentration of ethylenediamine vapour was tolerated for 15 minutes, but produced an asthmatic response after 4 hours, at which time FEV_1 was reduced by 26%. The FEV_1 continued to decrease over the next 3 hours towards a 40% reduction, and a 26% reduction was still apparent after 24 hours, despite treatment with bronchodilator drugs. This pattern of response to ethylenediamine was reproducible, and the subject did not respond similarly to any of a series of other irritant chemicals tested. Thus a clear pattern of asthmatic response that was apparently specific to ethylenediamine was observed in this study.

A number of other case reports are available of individuals who exhibited asthmatic signs and symptoms associated with exposure to ethylenediamine in the workplace (Gelfand, 1963; Nakazawa and Matsui, 1990; Ng *et al*., 1991). Although bronchial challenge testing with ethylenediamine produced asthmatic responses in these subjects, they had personal and/or family histories of allergic disease and/or they had worked with and responded on challenge to

other substances. Thus, these studies provide only supporting circumstantial evidence for the involvement of ethylenediamine in producing occupational asthma.

Retrospective studies using the medical records of populations of workers using ethylenediamine have indicated that about 10% of such populations developed signs and symptoms of occupational asthma; no challenge tests were carried out with these surveys (Aldrich *et al*., 1987; Lewinsohn and Ott, 1991).

SUPPORTING DATA

Only very limited data are available. In the study by Popa *et al* (1969), positive Prausnitz-Kustner transfer reactions (indicative of the presence of immunoglobulin E antibodies) were given by all four individuals with positive bronchial inhalation challenge tests. Negative findings were obtained in the subjects who did not respond to bronchial challenge.

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C12: GLUTARALDEHYDE

SUMMARY AND CONCLUSION

There is a mixed body of evidence relating to the potential of glutaraldehyde to cause occupational asthma. The positive evidence comprises small groups of cases supported by appropriate responses in bronchial challenge tests, and data reported by the Surveillance of work-related and occupational respiratory disease (SWORD) scheme. More than a hundred cases of glutaraldehyde-induced asthma have been recorded within SWORD, although some other surveys of contemporary workers have reported negative findings. The mechanism by which glutaraldehyde causes asthma is presently unclear, but may involve irritant and/or immunological components.

There is sufficient evidence to conclude that glutaraldehyde meets the revised EU criteria (1996) for classification as a respiratory sensitiser (a cause of asthma) and labelling with R42.

INTRODUCTION

Glutaraldehyde is used primarily as a biocide or chemical disinfectant, in particular as a cold sterilant of medical and surgical instruments (used at about 2%) and for inhibition of corrosion causing bacteria in offshore operations.

The following information has been summarised from an HSE Criteria Document for an Occupational Exposure Limit, where a more detailed critical appraisal of the available data can be found (Elliott-Minty *et al*., 1997).

EVIDENCE FOR WORK-RELATED ASTHMA

Reports of glutaraldehyde as a cause of occupational asthma largely originate from the health services sector. The irritancy of the liquid and vapour makes differentiation between primary irritant responses and asthmatic symptoms difficult.

Seven health-care workers who had developed asthma with characteristic latent periods reacted positively to glutaraldehyde in unblinded bronchial challenge testing (Gannon *et al*., 1995). A further 3 workers gave positive bronchial challenges in a related study (Curran *et al*., 1996). Other studies have confirmed occupational asthma induced by glutaraldehyde in 2 hospital staff, using bronchial challenges, one of which was performed single blind (Cullinan *et al*., 1992; Nicewitz *et al*., 1986). The only study including double-blind challenge testing involved a nurse who gave a negative result 8 months after exposure to glutaraldehyde had ceased; overall, it could not be established whether glutaraldehyde was or was not the cause of this nurse's asthma (Stenton *et al*., 1994). Other reports of occupational asthma due to glutaraldehyde have been compromised by the presence of pre-existing asthma, co-exposure to other chemicals or poor reporting.

Since 1989, a total of 113 cases of occupational asthma have been attributed to glutaraldehyde by diagnosing physicians participating in the SWORD scheme (e.g. Sallie *et al*., 1994). Similarly, the Department of Social Security has agreed disablement due to glutaraldehyde-induced asthma in 69 people since 1992 (HSC, 1996).

Although a modem cross-sectional study of Australian endoscopy nurses found no increase in respiratory symptoms, only current workers were studied, so that any previously leaving work due to ill-health would have been missed (Pisaniello *et al*., 1997). Other surveys (e.g. Teta *et al*., 1995) have suffered from a number of deficiencies of conduct and/or reporting, and therefore do not contribute significantly to the overall picture.

SUPPORTING DATA

Specific immunoglobulin E (IgE) has been found in 4/20 workers with respiratory symptoms attributed to glutaraldehyde (Curran *et al*., 1996).

No internationally validated animal tests are currently available that allow prediction of the ability of a chemical to induce asthma in humans. Regarding the investigations that have been conducted, glutaraldehyde failed to induce pulmonary hypersensitivity in guinea pigs (Werley *et al*., 1995). In contrast, the findings of IgE assays conducted in mice were indicative of the potential to cause respiratory allergy (Union Carbide, 1994).

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C13: SOME HARDWOOD DUSTS

SUMMARY AND CONCLUSION

There is evidence that exposure to some hardwood dusts can be associated with the development of occupational asthma, including positive findings in a number of specific bronchial challenge tests. Overall, the frequent detection of specific immunoglobulin E and the results of skin prick tests are generally supportive of an immunological reaction occurring in at least some workers, although it is not known whether this reaction is involved with the development of the asthma or is merely an indication of exposure to the wood dust.

There is sufficient evidence to conclude that some hardwood dusts (including, for example, palisander, iroko and African maple) meet the revised EU criteria (1996) for classification as respiratory sensitisers (causes of asthma) and labelling with R42.

INTRODUCTION

Hardwood dust is a general term covering a wide variety of wood dusts derived from angiosperms. There are some 12 000 species of trees world-wide, of which about 11 000 are hardwoods (IARC, 1995). Only about 40 species have been implicated in causing occupational asthma, and these belong to a range of families. Woods have a complex composition, with main structural components such as cellulose, polyoses and lignin, and a range of organic compounds known as ‘extractives’.

EVIDENCE FOR WORK-RELATED ASTHMA

Although there are several reports of occupational asthma associated with the use of hardwood dusts, only one has been investigated using a blinded bronchial challenge. A woman with no previous history of asthma developed asthmatic symptoms related to using palisander wood dust (Godnic-Cvar and Gomzi, 1990). When examined, she had been away from work for 3 months, and her airways did not show non-specific hyperresponsiveness. On single-blind challenge, she gave a late reaction to palisander involving a 26% decrease in forced expiratory volume in one second, but no reaction to oak dust. Several studies have been carried out in which open challenges have incorporated both control substances and normal or asthmatic controls. A woodworker with no history of atopy developed asthma after a latent period of one year; he then ceased work as a carpenter (Pickering *et al*., 1972). In a series of bronchial challenges conducted on different days, he failed to react to saline, kapor wood or western red cedar, but reacted to iroko wood dust challenge with late responses. One healthy and 3 asthmatic control subjects (including one with western red cedar-asthma) all failed to react to iroko.

Azofra and Olaguibel (1989) also reported a man who had iroko-associated rhinitis and asthma, which developed after a 5-month latent period, and whose airways were hyperresponsive to methacholine. He gave a positive response to iroko dust; 3 previously unexposed asthmatic patients failed to respond in control challenges. Another man developed asthma in association with exposure to African zebrawood (Bush *et al*., 1978). On different days he was challenged with a saline solution and extracts of zebrawood, white pine and western red cedar; he reacted only to the zebrawood. A previously unexposed asthmatic patient and a healthy control failed to react to this extract.

Four men with asthmatic symptoms all worked with African maple (obeche), two also with ramin (Hinojosa *et al*., 1986). Latent periods varied from 1 to 7 years. All underwent bronchial challenge with aerosols of the wood dust extracts, as did 2 non-exposed asthmatic subjects and 4 asymptomatic people exposed to the same woods. All 4 patients reacted to the African maple, three to the ramin; since two of these had not been previously exposed to ramin, it is likely that there was a cross-reaction between the two woods. Control challenges were negative. A craftsman who used a range of woods had a 20-year history of rhinitis and asthma associated

with using samba wood, which is another name for obeche (Innocenti and Angotzi, 1980). Bronchial challenge with samba sawdust, but not lactose, induced an early response in this man, but not in a non-asthmatic control. Lo Coco and colleagues (1987) reported that nasal irritation due to Mansonia walnut, which belongs to the same family as obeche, was fairly common in woodworkers, but asthma was unusual. They gave details of one joiner who developed asthma after a latent period of 7 years. He developed a biphasic asthmatic reaction on challenge with Mansonia walnut dust, but not with 3 other woods. Four normal subjects and one joiner previously exposed to Mansonia walnut apparently failed to react. One man with occupational asthma was exposed to obeche and oak at work (Malo *et al*., 1995). When challenged, he failed to react to obeche, but gave a positive response to oak. There were no controls in this study.

A man who had worked with wood for 30 years had a 5-6 year history of rhinitis and asthma when working with nara (Tochigi *et al*., 1983). Challenge with the wood dust but not with lactose induced an immediate response in the patient but not in a normal control. Similar reports with largely supportive evidence, although in small numbers of people, include Paggiaro *et al*., 1981 (Tanganyika aningre); Bush and Clayton, 1983 (Central American walnut); Colas *et al*., 1985 (Brazilian rosewood, iroko and “exotic sawdust”) and Basomba *et al*., 1991 (Pau Marfim).

In support of the above data, there are about a dozen small studies of people with occupational asthma in which open challenges were performed without the use of control subjects. These include Fasani *et al*., 1982 (Mansonia, ramin); Tahara, 1985 (boxwood); Maestrelli *et al*., 1987 (ebony); Gozalo Reques and Pelta Fernandez, 1988 (danta); Weber and Haussinger, 1988 (African maple); Malo and Cartier, 1989 (ash); Fabri *et al*., 1990 (Tanganyika, Mansonia, cherry); Hausen and Hermann, 1990 (Fernambouc); Kopferschmitt-Kubler *et al*., 1992 (ebony); Reijula *et al*., 1994 (obeche) and Szmidt and Gondorowicz, 1994 (ash). Most patients gave positive results at specific bronchial challenge.

One study revealed a clinical picture of extrinsic allergic alveolitis in a patient exposed to African maple (Hinojosa *et al*., 1984), and two other reports support this finding in other individuals (Howie *et al*., 1976 with ramin; Innocenti *et al*., 1991 with cabreuva).

The prevalence of pulmonary obstructive airways disease, which would include asthma, has been studied in 817 hardwood workers who were exposed primarily to maple, and minimally to ash and oak (Whitehead *et al*., 1981). Abnormal pulmonary function measurements consistent with obstructive disease were found in 26-30% of workers. When current or past smokers were excluded, to avoid confounding by chronic bronchitis, 12-17% of workers had these changes; the prevalence of asthma was not determined.

Another study of limited value measured lung function in groups of workers exposed to a range of hardwoods (Goldsmith and Shy, 1988). Chronic symptoms such as breathlessness or wheeze were not significantly increased compared to an unexposed control group, although change in peak flow correlated significantly with wood dust exposure. Nose and eye irritation were increased in the exposed population.

The Surveillance of Work-related and Occupational Respiratory Disease scheme records an average of 21 cases of occupational asthma associated with wood dusts each year, about half of which are due to hardwood (Meredith and McDonald, 1994; Sallie *et al*., 1994).

SUPPORTING DATA

Specific immunoglobulin E (IgE) to wood dust extracts has been found in a good number of cases of occupational asthma, often correlating with positive bronchial challenge results, as in Bush *et al*., 1978 (African zebrawood); Fasani *et al*., 1982 (various woods); Tochigi *et al*., 1983 (nara); Hinojosa *et al*., 1984; Hinojosa *et al*., 1986 (both African maple); Weber and Haussinger, 1988 (African maple); Fabri *et al*., 1990 (Tanganyika aningre); Basomba *et al*., 1991 (Pau Marfim); Reijula *et al*., 1994 (obeche). However, negative results have also been obtained, as in Paggiaro *et al*., 1981 (Tanganyika aningre); Fasani *et al*., 1982 (various woods); Bush and Clayton, 1983

(walnut); Carosso *et al*., 1987 (various woods); Malo and Cartier, 1989 (ash); Reijula *et al*., 1994 (obeche).

Skin prick tests have often been positive, correlating with asthma or positive bronchial challenge, as in Pickering *et al*., 1972 (iroko); Bush *et al*., 1978 (African zebrawood); Innocenti and Angotzi, 1980 (samba); Paggiaro *et al*., 1981 (Tanganyika aningre); Fasani *et al*., 1982 (various woods); Tochigi *et al*., 1983 (nara); Hinojosa *et al*., 1984 (African maple); Colas *et al*., 1985 (various woods); Tahara, 1985 (boxwood); Hinojosa *et al*., 1986 (African maple); Carosso *et al*., 1987 (obeche); Gozalo Reques and Pelta Fernandez, 1988 (danta); Weber and Haussinger, 1988 (African maple); Fabri *et al*., 1990 (various woods); Godnic-Cvar and Gomzi, 1990 (palisander); Basomba *et al*., 1991 (Pau Marfim); Reijula *et al*., 1994 (obeche) and Szmidt and Gondorowicz, 1994 (ash). Negative tests have also been reported, including Bush and Clayton, 1983 (walnut); Colas *et al*., 1985 (various woods); Maestrelli *et al*., 1987 (ebony); Azofra and Olaguibel, 1989 (iroko) and Fabri *et al*., 1990 (various woods). Of particular interest is a study of bowmakers exposed to fernambouc, with 35 out of 36 giving negative skin prick responses (Hausen and Herrmann, 1990). Similarly, Soriani and D'Andrea (1984) obtained only 3 positive tests for various woods among 16 subjects who suffered from asthma without bronchitis, and 0/10 in those with asthma and bronchitis. In another study, more patients with asthma or bronchitis associated with various woods were given skin prick tests, and only 29/101 were positive (Kirsten *et al*., 1985).

Total IgE has been raised in some cases, as in Tochigi *et al*., 1983 (nara); Colas *et al*., 1985 (various woods); Hinojosa *et al*., 1986 (African maple); Weber and Haussinger, 1988 (African maple); Azofra and Olaguibel, 1989 (iroko); Basomba *et al*., 1991 (Pau Marfim) and Reijula *et al*., 1994 (obeche).

No studies are available of specific IgE or skin prick tests in exposed subjects without asthma.

Passive transfer of antibodies into healthy humans has been demonstrated in 3 studies; Tochigi *et al*., 1983 (nara); Hinojosa *et al*., 1984 (African maple); (Gozalo Reques and Pelta Fernandez, 1988 (danta). Two incidents of urticarial rashes have also been reported (Goransson, 1980 with Phillipine red mahogany; Hinojosa *et al*., 1990 with African maple).

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C14: ISOCYANATES

SUMMARY AND CONCLUSION

There is a strong body of evidence that isocyanates cause occupational asthma in a significant proportion of exposed workers. An immunological response appears to be involved in at least some people, although a direct effect on the airways has also been postulated.

There is sufficient evidence to conclude that isocyanates meet the revised EU criteria (1996) for classification as respiratory sensitisers (causes of asthma) and labelling with R42.

INTRODUCTION

This assessment has drawn largely on recent reviews of the literature on isocyanates and asthma, together with some use of primary reports.

Isocyanates are widely used in the manufacture of polyurethane foams, plastics, coatings and adhesives, with an estimated global production of 5 million tons in 1990 (Baur, 1990). Just 3 diisocyanates; diphenylmethane 4,4' diisocyanate (MDI), toluene diisocyanate (2,4-TDI and 2,6-TDI) and hexamethylene diisocyanate (HDI) account for greater than 90% of this commercial use. The use of monoisocyanates is limited (Baur *et al*., 1994; Kennedy and Brown, 1992). Isocyanates are very reactive, binding readily to proteins, and hydrolyse rapidly in aqueous environments to diamines (Baur *et al*., 1994). Isocyanates are irritant, and at high exposure levels cause damage to airway epithelia (Baur *et al*., 1994, Kennedy and Brown, 1992).

EVIDENCE FOR WORK-RELATED ASTHMA

It has been reported that isocyanates are the leading cause of occupational asthma in the Western World (Hayes and Newman Taylor, 1995). A significant proportion of isocyanate-exposed workers are affected by symptoms of bronchial asthma, and there is a lower prevalence of rhinitis, conjunctivitis, bronchitis and obstructive airway disease (Baur *et al*., 1994). Urticaria, fever and extrinsic allergic alveolitis can also occur, but rarely. The estimated prevalence of asthma is 5 - 10%, although 30% has been found in some studies. There is a latent period, with 60% of affected workers developing asthma within 5 years. There is no evidence that atopy or smoking influences a person's susceptibility to developing asthma. It is clear that isocyanates can trigger asthmatic responses at relatively low concentrations, with some individuals responding to extremely low concentrations. However, not all symptomatic people react to bronchial challenge with the isocyanate to which they are exposed at work; possibly, given that many people handle isocyanates for hours before developing symptoms, a cumulative exposure may be necessary. In other studies, local morphological changes consistent with airway inflammation have been noted.

There are a few reports that include blinded bronchial challenge tests. Sixty-three workers, all of whom had a history suggesting isocyanate asthma, underwent blinded bronchial challenge with non-irritant concentrations of TDI or occasionally MDI or HDI (Banks *et al*., 1989). A positive challenge occurred in 30 (48%) people. There were no apparent differences between responders and non-responders in terms of their latent period or duration of exposure. Thirty-one people had airways that were hyperresponsive to methacholine; 68% of these reacted at specific bronchial challenge.

One man who had developed occupational asthma after being 'drenched' with TDI in an accident, avoided exposure for 11 years (Banks and Rando, 1988). He then underwent blinded bronchial challenge, which was negative. He resumed work with isocyanates, and within 3 months his occupational asthma recurred; he also gave a positive reaction at blinded challenge with TDI at this time.

In an early study, 4 non-atopic patients with TDI-associated occupational asthma were exposed to varnish with and without a TDI-containing activator (Pepys *et al*., 1972). The tests were apparently performed in a blinded manner. All patients reacted to the varnish with the activator, with decreases in forced expiratory volume in one second (FEV_1) of 20 - 70%, but not to the varnish without it. Two healthy and one asthmatic control subjects, not previously exposed to TDI, failed to react in similar challenge tests.

A patient with occupational asthma, who was suffering nocturnal attacks with decreases in FEV_1 of about 24%, underwent blinded challenge with TDI, which caused a dual response involving FEV_1 decreases of 55% and 42% (Banks *et al*., 1986). The following day he underwent mock challenge, and developed a late (nocturnal) response consisting of a 40% decrease in FEV_1. However, it is not possible to tell whether this particular subject had a genuine response to the placebo, or suffered his “normal” nocturnal attack exacerbated by his exposure to TDI the day before.

A number of normal or asthmatic controls have been challenged with isocyanates and have generally given negative responses (Butcher *et al*., 1976; Pezzini *et al*., 1984). However, in control groups of 10 normal and 14 asthmatic subjects not previously exposed to isocyanate, one and three respectively gave early responses to specific challenge with TDI (Vogelmeier *et al*., 1991). This finding apparently indicates that under certain circumstances isocyanates can directly affect the airways of those not previously exposed.

SUPPORTING DATA

Specific immunoglobulin E (IgE) antibodies have been detected in some workers exposed to isocyanates. In one review, 148 (14%) of 1095 workers who had asthmatic symptoms also had specific IgE to at least one of the 3 common isocyanates (Baur *et al*., 1994). Only 1 of 685 workers without symptoms had such antibodies. There was a good correlation between the presence of specific IgE and positive skin prick tests. It had earlier been noted that measurement of specific IgE was total IgE dependent, and that this had to be taken into account when determining a result (Baur, 1990). It has also been suggested that the prevalence of specific IgE may be underestimated, since the detection assay which usually uses 2,4-TDI may not adequately pick up antibodies to the isomer 2,6-TDI (Karol and Jin, 1991). Using a reportedly more sensitive assay, 27% (6/22) of symptomatic workers were found to have specific IgE to TDI, and 83% (5/6) to MDI; 3 of the latter had been exposed to accidental “high” concentrations of MDI (Pezzini *et al*., 1984). Those developing occupational asthma within 6 years of first exposure were more likely to have specific IgE antibodies than those developing it later. In contrast to the results for IgE, similar levels of IgG were reported for exposed workers whether (24%) or not (17%) they had symptoms (Baur *et al*., 1994).

In addition to producing an immunological response in some individuals, isocyanates and their hydrolysates have a direct constrictive effect on bronchial smooth muscle, as detected both in animals and *in vitro*, resulting in hyperresponsive reactions to acetylcholine. There are indications that neuropeptides and tachykinins play a part in this response (Baur *et al*., 1994; Hayes and Newman Taylor, 1995). However, the high concentrations of isocyanates used in some of the animal studies could have caused airway damage.

Although no internationally-validated predictive animal tests are currently available, animal models, usually involving guinea pigs, have been employed to investigate the ability of isocyanates to induce respiratory responses. In one study, induction by inhalation or dermal routes with free TDI or tolylmonoisocyanate (TMI) has been followed by inhalation challenge with either a serum albumin conjugate (for TMI) or free isocyanate (for TDI), and positive responses were obtained (Karol 1986). Moderately high concentrations were needed at induction and challenge. Antibodies were detected in the guinea pigs exposed to TDI, but it was unclear from the report what proportion of these were allergic to antibody.

In another experimental assay system, MDI caused an increase in serum levels of IgE in mice exposed topically (Kimber and Dearman, 1992).

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C15: LABORATORY ANIMAL EXCRETA/SECRETA

SUMMARY AND CONCLUSION

The findings of several epidemiological studies and data reported by the Surveillance of work-related and occupational respiratory disease (SWORD) scheme indicate that occupational asthma can occur in a significant number of people who work with laboratory animals. The asthma is generally part of an allergic condition that also involves other symptoms such as rhinitis. Although bronchial challenge data are limited in relation to the prevalence of the asthma, positive results have been obtained in several studies. There is evidence of immunological reactions occurring in some asthmatic individuals, but their relationship to symptoms is unclear.

There is sufficient evidence to conclude that animal excreta/secreta meets the revised EU criteria (1996) for classification as a respiratory sensitiser (a cause of asthma) and labelling with R42.

INTRODUCTION

Reports that laboratory animals workers suffer from an allergy to the animals with which they work are numerous (Moller, 1990; Bardana, 1992; Newman Taylor and Gordon, 1993). Many small mammals are implicated, as are insects such as locusts, but the majority of workers are affected by rats and mice, which may reflect the use pattern. Proteinaceous excreta and secreta of the animals are the major source of allergens, which include several proteins present in rodent urine (Moller, 1990; Newman Taylor and Gordon, 1993). The allergic condition presents as rhinitis, conjunctivitis, contact urticaria and asthma. Allergy to cats and dogs has also been reported, but because contact may occur outside of work it is not often possible to determine if such an allergy is occupational (Moller, 1990).

EVIDENCE FOR WORK-RELATED ASTHMA

Accounts of bronchial challenge tests in the published literature are rare. Five atopic laboratory animal workers, one a previous sufferer from asthma, had developed asthma after working with rats and mice, with latent periods up to 4 years (Newman Taylor *et al*., 1977). They underwent bronchial challenge with a control physiological solution, a range of rat and mouse products (urine extract, urine protein fractions, serum, hair extract), dust from cages, and handling rats, with each challenge on a separate day. It is unclear whether the challenges with the extracts or proteins were performed in a blinded manner. All 5 reacted positively to urine extracts or protein fractions, and 3/5 to sera. At least one reacted to the cage dust and to the rat (reaction of others not stated), but none reacted to hair extract. Overall, the study provides evidence that working with rodents can induce asthma, as indicated by reaction at specific bronchial challenge in affected individuals.

A two-part study was carried out on groups of animal workers who had work-related allergy, with apparently little or no overlap between the groups (Eggleston *et al*., 1990; Eggleston *et al*., 1995). Not all subjects had asthma, about half had airways that were hyperresponsive to methacholine, and almost all were atopics. In the first study, atopics without animal allergy acted as controls. Occupational challenge was carried out in a rat animal house, with the subject cleaning cages or standing near them being cleaned (high exposure), or sitting in the cleaning area while no cleaning was being carried out (low exposure). Study two had a third group who were “sham exposed” in a rat-free atmosphere, but details were not given. In the first study, 2/12 subjects but no controls (0/5) had positive bronchial reactions, as indicated by a fall in forced expiratory volume in one second of greater than 15%. In the second study, 6/17 reacted at the high exposure, 5/17 at the low exposure and none during the sham exposure; chest symptoms were more severe at the higher dose. Again, these findings indicate that exposure to rat excreta can cause specific asthmatic responses.

A number of good-quality epidemiological studies have been conducted involving groups of 100-400 British subjects (Davies *et al*., 1983; Botham *et al*., 1987; Venables *et al*., 1988; Cullinan *et al*., 1994) and 5641 Japanese (Aoyama *et al*., 1992). Although in most investigations symptoms were assessed only by self-completed questionnaire, Botham and colleagues (1987) obtained clinical confirmation when the chest was affected. Prospective studies indicated that up to 2% of workers develop asthmatic symptoms during their first year of employment (Davies *et al*., 1983; Botham *et al*., 1987). Cross-sectional studies found between 7 and 11% of workers with asthmatic symptoms, developing mostly during the first three years of exposure (Venables *et al*., 1988; Aoyama *et al*., 1992; Cullinan *et al*., 1994). Asthmatic symptoms did not occur in the absence of other allergic symptoms such as rhinitis. There were indications that more atopics developed the disease during their first year of exposure, but this difference levelled out thereafter (Botham *et al*., 1987).

The SWORD scheme recorded 21 cases of occupational asthma associated with animal work for the UK in 1989, giving an estimated incidence of 204 cases per million laboratory technicians and assistants, some of whom would not work with animals but might be exposed to other asthmagens (Meredith *et al*., 1991; Newman Taylor and Gordon 1993). In 1993, 34 cases were reported by SWORD (Sallie *et al*., 1994).

SUPPORTING DATA

There is evidence of immunological reactions occurring in association with the presence of laboratory animal allergy, although many of the data refer to allergy rather than to asthma. In a cross-sectional study, 63% of people with chest symptoms had positive skin prick tests to an extract of rat urine, compared with only 5% of those without chest symptoms (Cullinan *et al*., 1994). Newman Taylor (1977) found general agreement between the results of skin prick and bronchial challenge tests. Thirteen per cent of workers with laboratory animal allergy gave positive responses to skin prick tests to one or more urine extracts, and 38% had specific immunoglobulin E (IgE) to urine extract (Venables *et al*., 1988). Although high proportions of allergic subjects have been found to have specific IgE to rat urine extracts, the levels of specific IgE did not correlate with either symptoms or degree of exposure (Platts-Mills *et al*., 1987; Eggleston *et al*., 1990; Eggleston *et al*., 1995). Other investigators have found a poor correlation between the presence of IgE antibodies to a rat urine allergen and symptoms (Botham *et al*., 1987). The pattern of IgG responses has been found to be complex, with raised levels being related more to the presence of clinical symptoms and specific IgE rather than to the degree of exposure (Price and Longbottom, 1989). Thus allergy to laboratory animals is associated with immunological reactions, but their relationship to symptoms is unclear.

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C16: LATEX

SUMMARY AND CONCLUSION

A considerable number of reports indicate that latex can cause occupational asthma. Although the available bronchial challenge data have not been generated using the most stringent protocols, overall they provide reasonable evidence that latex can induce asthma, and the common occurrence of specific immunoglobulin E (IgE) and positive skin prick tests to latex in affected individuals suggests an immunological mechanism for this induction.

Most of the available reports concern asthma that is associated with exposure to latex gloves, particularly among health care workers, and it is generally not possible to ascertain if the induction phase of any immunological response occurred by inhalation or skin contact with the latex. For the latter route, asthma may be one manifestation of a generalised systemic effect.

There is sufficient evidence to conclude that latex meets the revised EU criteria (1996) for classification as a respiratory sensitiser (a cause of asthma) and labelling with R42.

INTRODUCTION

Natural rubber (latex) is found in *Hevea braziliensis*, a tree originating from the Amazonian region. Reports of immediate hypersensitivity to natural latex have been published, mainly since 1979 (Tarlo *et al*., 1990). Most of these consist of cases of contact urticaria, together with a few reports of allergic rhinitis or anaphylaxis. Recent evidence suggests that a constituent of rubber latex is easily liberated into the atmosphere, and the subsequent appearance of asthmatic symptoms has been linked to this phenomenon (Hopkins, 1995).

EVIDENCE FOR WORK-RELATED ASTHMA

Seaton *et al* (1988) described the case of a laboratory technician with a 2-year history of increasingly troublesome attacks of cough and wheeze. Peak flow rates were greater during a holiday than at work. Challenge with talc or glove starch produced no reaction, but a 40% drop in peak flow was observed within 15 minutes of a short period of putting on and removing latex gloves.

Lagier *et al* (1990) reported on a nurse who had a history of wearing latex gloves for several years and in whom symptoms of asthma developed in an operating room when she was not wearing gloves. A non-specific challenge test conducted with carbamylcholine demonstrated bronchial hyperresponsiveness. Exposure of the subject to the effect of someone else putting on and removing vinyl gloves produced no bronchial reaction, but when this was repeated with latex gloves, the forced expiratory volume in one second (FEV_1) fell by 22%. This represented an immediate asthmatic reaction to latex particles.

A latex glove inspector was assessed for occupational asthma by Tarlo *et al* (1990). Asthmatic symptoms began within 10 minutes of the onset of work, completely cleared during a holiday and recurred on return to work. The peak flow was reduced at work in comparison with values obtained at home. The results of a methacholine challenge test indicated severe airway hyperresponsiveness. Bronchial challenge with cornstarch glove powder and a coagulant proved negative. A subsequent evaluation was undertaken of most of the workforce in the surgical glove manufacturing plant. The company employed 87 workers, of which 81 took part in the study. A questionnaire was completed by 68 workers, and 52 of them described respiratory symptoms at work. Pulmonary function tests conducted in 50 of these demonstrated a drop in FEV_1 of 15% or more during a workshift in 5 subjects. Methacholine challenge was carried out on a work day in 11 workers and showed a response in the asthmatic range in 5 cases. A diagnosis of latex occupational asthma was made for 3 workers, including the initial case.

An operating room nurse became asthmatic following the use of latex surgical gloves (Marcos *et al*., 1991). Symptoms occurred within 10-15 minutes of starting work and disappeared on days away from surgery. Changes in the peak expiratory flow rate of 15% or more were detected on work days. The results of methacholine challenge indicated bronchial hyperresponsiveness. Apparently unblinded bronchial challenge with latex glove extract demonstrated an immediate response, with FEV_1 decreasing by 44% at 15 minutes and returning to baseline 2 hours later. Phosphate buffered saline showed no such response, and latex challenges in 2 control asthmatic patients with similar nonspecific reactivity to the test subject were also negative.

Several cases of exposure to occupationally inhaled latex have briefly been reported by Sussman *et al* (1991). In the first, a dental assistant presented with a history of nasal and eye symptoms along with wheezing and shortness of breath when around latex gloves stopped work because of asthma. In the second, a laboratory technician experienced rhinitis, conjunctivitis and cough at work. The symptoms cleared at weekends and during holidays. Non-latex gloves were used to allow continuation at work, but asthma treatment was still required due to the presence of latex aerosolised from the gloves of other workers. Finally, a dialysis nurse had to discontinue work because of latex-induced asthma.

A cook developed contact urticaria, nasal symptoms and laboured respiration when exposed to rubber gloves during work (Kanny *et al*., 1992). The symptoms appeared a few minutes after putting on gloves and disappeared 30 minutes after taking them off. Peak expiratory flow was normal. The findings of a carbamylcholine challenge test indicated bronchial hyperresponsiveness. An apparently unblinded bronchial challenge test was conducted using a spray containing distilled water previously used for rinsing a latex glove. Within 2 minutes sneezing, rhinorrhoea, cough and dyspnoea were noted, and the peak expiratory flow fell by 27%.

Baur *et al* (1992) studied 56 subjects who displayed symptoms on contact with latex and gave immediate reactions against latex milk in skin prick tests. The group included 52 hospital staff and 4 with other employment. All suffered from contact urticaria, 12 also had symptoms of rhinitis or conjunctivitis and 24 had shortness of breath. In 23 cases, where subjects had a history of dyspnoea and symptoms of rhinitis and/or conjunctivitis, a workplace-related exposure test was conducted with powdered latex gloves. Symptoms were reproduced in 19/23 of these subjects and 6/23 showed significant respiratory obstruction, as indicated by a rise of over 100% in specific respiratory resistance.

Jaeger *et al* (1992) evaluated 70 patients with contact urticaria to latex. Almost all had worked in a medical environment. Some of these may have been included in the study of Baur *et al* (1992), described above. In the present study, 36 had rhinitis, 31 conjunctivitis and 22 dyspnoea. Single-blinded bronchial challenge was performed in 18 subjects with dyspnoea or rhinitis/conjunctivitis related to latex exposure and latex specific IgE. Latex-free gloves were worn underneath the test article to prevent local penetration of latex antigens. A significant increase in specific airway resistance of at least 100% occurred in 5 cases on exposure to latex gloves, and no significant reaction was observed when latex-free gloves were used.

A nurse working on a dialysis unit observed urticaria and rhinorrhoea when wearing latex gloves (De Zotti *et al*, 1992). Despite a change to wearing non-latex gloves next to the skin, the symptoms persisted, mainly during contact with other nurses who wore latex gloves. Symptoms worsened with the development of dry cough, shortness of breath and wheezing. Peak flow rate at work fell by up to 37% when working in dialysis. After wearing one latex glove for 10 minutes a rapid fall in FEV_1 occurred, indicating an immediate bronchospasm.

In a study of 49 employees of a medical centre, 36 had rhinoconjunctivitis and 13 had asthma thought to be related to latex exposure (Bubak *et al*, 1992). Lung function and challenge tests were not performed.

A nurse working in an infant clinic developed urticaria, rhinitis, conjunctivitis and at a later stage, bronchial asthma, in association with exposure to latex containing products (Baur *et al*, 1993). Nine months after ceasing work, the subject was symptom-free but hyperresponsive to methacholine. Spirometry values were in the normal range. A workplace inhalation test revealed mild eye and nasal symptoms with latex-free gloves and severe rhinitis and conjunctivitis on exposure to latex gloves. Lung function tests showed no significant increase in the preexisting airway obstruction.

In a study of 5 health care workers with exposure to latex, 3 had bronchospasm (Rosen *et al*, 1993). No lung function or challenge tests were conducted.

A nurse who often wore latex gloves during work in a liver transplant department developed a number of work-related allergic symptoms, including dry cough, laboured respiration and wheezing (Chatte *et al*, 1993). The symptoms disappeared during holidays and when hypoallergenic latex gloves were worn. The findings of spirometry were normal, but testing with carbamylcholine demonstrated non-specific bronchial hyperresponsiveness. Apparently unblinded challenge with latex gloves produced a 42% drop in FEV_1 within 5 minutes, while no changes were obtained on challenge with lysoformine spray, ethylene oxide or hypoallergenic latex gloves.

Jaeger *et al* (1993) assessed 14 subjects (11 working in the medical field) who displayed symptoms of immediate-type allergy to latex gloves and had specific IgE antibodies. Rhinoconjunctivitis was observed in all and dyspnoea in 10 cases. In a methacholine test, 6 of the 12 people examined showed excessive bronchoconstriction, 2 showed a marginal increase in respiratory resistance and one individual had obstruction at rest. No methodological details were provided. A workplace nasal challenge test was conducted in which subjects manipulated vinyl gloves followed by latex gloves, whilst wearing plastic gloves to prevent skin contact with latex. Some degree of nasal reaction was noted in response to handling latex in all 12 subjects tested. One individual suffered an asthmatic attack, one showed significant and another slight respiratory tract obstruction. Apparently unblinded bronchial challenges using glove washing solution were positive, as indicated by an increase of more than 100% in specific airway resistance, in 6 of the 7 symptomatic subjects tested. Responses of 2 patients without a history of dyspnoea were no different from 3 control subjects who did not have latex allergy. Initial control tests with saline did not produce positive responses.

Moneret-Vautrin *et al* (1994) described 2 cases of reactivity to latex. In the first, a nursing assistant developed dyspnoea following the use of latex gloves. After a period during which latex was avoided, re-exposure led to severe rhinoconjunctivitis and dypnoea after a few minutes. Non-specific bronchial hyperresponsiveness was detected in a carbamylcholine challenge test. A single-blind challenge test with the subject wearing vinyl gloves did not produce a reaction. Use of latex gloves resulted in dyspnoea after 25 minutes accompanied by a 30% drop in FEV_1. Bronchial challenge with latex solution resulted in bronchospasm with a fall in FEV_1. The second case, a laboratory technician, developed rhinitis in association with the wearing of latex gloves. No lung function or challenge tests were conducted on this subject.

Orfan *et al* (1994) have evaluated occupational asthma in a latex doll manufacturing plant. The study stemmed from observations on a single employee who developed watery eyes, rhinorrhoea, chest tightness and wheezing on entering an area where doll parts were being sanded. A workplace challenge was conducted, ensuring that skin absorption of latex protein was not possible. Whilst in a room next to the sanding area, wheezing and shortness of breath occurred at 15 minutes and FEV_1 fell by 65% when compared with the baseline value. In 13 workers exposed to unsanded doll parts, none complained of symptoms. Two of 9 workers in or near the sanding room displayed asthmatic symptoms, including the subject who caused the initial concern.

Four nurses investigated by Pisati *et al* (1994) had contact urticaria to latex gloves. Despite wearing non-latex gloves underneath or instead of latex gloves, all suffered asthmatic attacks. In 2 nurses a fall of at least 20% in FEV_1 was documented during a workshift. The results of methacholine challenge tests indicated bronchial hyper-responsiveness in all cases. Each nurse was challenged by the handling of latex gloves used at work. Immediate bronchoconstriction was seen in all cases, with a fall in FEV_1 of at least 20%. Challenge with pure cornstarch powder did not produce a reaction. Specific bronchial challenges with nebulised materials were also conducted, apparently in an unblinded fashion. In 2 of the 4 nurses a fall in FEV_1 of at least 15% from baseline value was obtained with non-powdered latex glove extract, and all 4 produced such a response with powdered latex glove extract. Exposure to cornstarch powder extract did not induce a reaction.

Four subjects (2 nurses, 1 laboratory technician, 1 dental assistant) regularly exposed to latex gloves all developed asthmatic symptoms (Valentino *et al*, 1994). In each case, baseline lung function tests were found to be normal. Methacholine challenge tests demonstrated bronchial hyperresponsiveness. One of the nurses underwent workplace challenge involving a colleague manipulating gloves in front of her. Vinyl gloves failed to induce a response whereas latex gloves caused a drop in FEV_1 of 24%.

Vandenplas *et al* (1995a) studied the prevalence of occupational asthma due to latex among hospital employees. Initially, 289 subjects were recruited, 273 of whom completed a questionnaire and had a skin prick test to latex. Non-specific and specific challenges were performed on 12 of the 13 subjects who gave positive skin prick tests. Five of these had a history of occupational asthma. All 12 were hyperresponsive according to the results of histamine challenge tests. Specific challenge was carried out by firstly asking individuals to handle vinyl gloves as a control exposure. Secondly, whilst wearing vinyl gloves to prevent skin exposure to latex, they were requested to handle latex gloves. A positive reaction to latex, indicated by a sustained fall in FEV_1 of at least 20%, was observed in 7 subjects, consisting of 4 immediate and 3 dual responses, and included those with asthma.

In a second study, the same group carried out similar tests on 8 health care workers with a history of latex glove related asthma (Vandenplas *et al*, 1995b). Challenge with histamine revealed bronchial hyperresponsiveness in all cases. Specific challenge testing was also positive in all subjects, producing 5 immediate and 3 dual reactions.

In a study by Hunt *et al* (1995), 104/342 health care workers were considered to be allergic to latex. Forty one percent of the allergic group experienced asthmatic symptoms when working in areas where large numbers of latex gloves were used. Fifteen percent of latex allergic patients had respiratory symptoms without ever having had contact urticaria.

SUPPORTING DATA

A nurse with suspected allergy to latex was evaluated by Ahman and Wrangsjo (1994). Following the occurrence of contact urticaria when wearing latex gloves, the subject began using non-latex gloves. However, more sneezing, nasal running and blockage, cough, skin rash and itching appeared. A test for specific IgE to latex was weakly positive, and a skin prick test with latex extract was positive. Nasal peak flow rates decreased and nasal symptoms increased on work days. A challenge test was conducted with the subject putting on and removing latex gloves as well as shaking them in front of her nose. Nasal blockage occurred within 5 minutes and serial nasal peak flow rates showed immediate nasal obstruction.

In a study of 56 patients (53 with possible occupational exposure to latex) with a positive skin prick test to latex milk, 50/56 demonstrated latex specific IgE (Baur *et al*., 1992). In a similar study of 70 patients by the same group (Jaeger *et al*., 1992), latex specific IgE was found in 62%. The corresponding figure for 22 patients with dyspnoea was 82%. A positive skin prick test using natural latex milk was recorded in 38 of 45 tested.

In a study of 49 medical centre employees with possible latex allergy, latex specific IgE was found in 19/35 tested and skin prick tests with latex products were positive in 34/49 (Bubak *et al*., 1992).

In a study of 14 subjects with symptoms of latex allergy, including 11 individuals from medical professions, a positive skin prick test to latex allergen was observed in all cases (Jaeger *et al*., 1993). Nasal challenge with powder scratched off latex gloves produced a clinical nasal reaction in 11/12 tested. In one case, asthma occurred and in 3 others slight bronchial obstruction was noted. Use of latex allergen-free glove powder in this test did not show a significant drop in nasal flow in any case.

A positive skin prick test to industrial latex solution was found in a latex glove inspector with symptoms of asthma (Tarlo *et al*., 1990). Subsequent evaluation of most of the workforce revealed 7 positive skin prick tests out of 64 workers evaluated.

Orfan *et al* (1994) have studied 22 employees of a latex doll manufacturing plant. A negative skin prick test with latex was found in 13 workers exposed to unsanded doll parts. A positive skin prick test was demonstrated in 2/9 subjects working in or near the sanding room. The authors also described another patient who complained of rhinorrhoea and wheezing related to the grinding of latex moulding on industrial machinery. This individual had a positive skin prick test to raw latex extract.

A considerable number of studies have reported the presence of latex-specific IgE and/or positive skin prick tests in association with exposure to latex in individuals or small numbers of cases (Lagier *et al*., 1990; Marcos *et al*., 1991; Sussman *et al*., 1991; De Zotti *et al*., 1992; Kanny *et al*., 1992; Baur *et al*., 1993; Chatte *et al*., 1993; Rosen *et al*., 1993; Moneret-Vautrin *et al*., 1994; Pisati *et al*., 1994; Valentino *et al*., 1994; Holm *et al*., 1995; Vandenplas *et al*., 1995b).

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C17: MALEIC ANHYDRIDE

SUMMARY AND CONCLUSION

Evidence that maleic anhydride can cause work-related asthma is provided by six cases in which bronchial challenge testing demonstrated that it was likely to have been the inducing agent. Supporting evidence is provided by its close structural relationship to phthalic anhydride and trimellitic anhydride, substances for which there is a substantial body of information indicating a causal association with asthma. No information is available on the involvement of the immune system in the development of maleic anhydride-related asthma.

There is sufficient evidence to conclude that maleic anhydride meets the revised EU criteria (1996) for classification as a respiratory sensitiser (a cause of asthma) and labelling with R42.

INTRODUCTION

Maleic anhydride is a versatile chemical intermediate which has applications in a wide range of commercial products. The principal use of the substance is in the manufacture of unsaturated polyester resins. Other uses include the manufacture of oil additives and maleic acid.

The following information has been summarised from an HSE Criteria Document for an Occupational Exposure Limit, where a more detailed critical appraisal of the available data can be found (Ridgway *et al*., 1996).

EVIDENCE FOR WORK-RELATED ASTHMA

Graneek *et al* (1986) reported four cases of asthma in workers exposed to maleic anhydride. Unfortunately, no clinical or exposure histories were presented. Three of the workers showed a late asthmatic reaction and increased responsiveness to histamine following bronchial challenge to maleic anhydride. The fourth worker was negative in the challenge test.

The airway responsiveness of two workers with asthmatic symptoms associated with exposure to maleic anhydride was investigated by well-conducted bronchial challenge testing (Durham *et al*., 1987; Graneek *et al*., 1987). Both subjects were described as atopic, but clinical or exposure histories were not provided. They both showed dual (i.e. immediate and late) asthmatic responses to maleic anhydride challenge as well as increased responsiveness to histamine at 3 and 24 hours after this challenge.

The cause of work-associated asthma in an individual exposed to both maleic anhydride and phthalic anhydride has been investigated (Lee *et al*., 1991). Asthmatic symptoms developed within a month of being involved in the loading of chemicals, which included these anhydrides, into reactors at a resin manufacturing plant. There was no previous personal or family history of asthma, although there was a history of vasomotor rhinitis; the individual was a heavy smoker. Relief of symptoms occurred when the individual was transferred to other sections within the plant. Well-conducted bronchial challenge tests were performed with phthalic anhydride and maleic anhydride. Phthalic anhydride elicited no response. In contrast, maleic anhydride provoked immediate and late asthmatic responses; the immediate response was accompanied by rhinitis and lacrimation. The worker also had non-specific airway hyperresponsiveness, as assessed by histamine challenge.

There are two further published cases of asthma in workers exposed to maleic anhydride, but the evidence of a causal relationship with maleic anhydride was not conclusive (Guerin *et al*., 1980; Gannon *et al*., 1992).

SUPPORTING DATA

No information is available on the involvement of the immune system in the development of maleic anhydride-related asthma.

Maleic anhydride is structurally related to phthalic anhydride and trimellitic anhydride, substances for which there is a substantial body of evidence of a causal association with asthma.

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C18: METHYL-TETRAHYDROPHTHALIC ANHYDRIDE

SUMMARY AND CONCLUSION

Several studies on methyltetrahydrophthalic anhydride (MTHPA) indicate that it can induce occupational asthma, although the findings of the available bronchial challenge tests are of limited value. Immunological data suggest an allergic mechanism for induction of the asthma, although antibody responses often correspond to exposure rather than symptoms. Supporting evidence is provided by the close structural relationship to phthalic anhydride, for which there is a substantial body of information indicating a causal association with asthma.

There is sufficient evidence to conclude that methyltetrahydrophthalic anhydride meets the revised EU criteria (1996) for classification as a respiratory sensitiser (a cause of asthma) and labelling with R42.

INTRODUCTION

Methyltetrahydrophthalic anhydride (MTHPA) is one of the acid anhydrides, which are irritant to eyes, skin and respiratory mucosa (Venables, 1989). It acts as a cross-linking agent in the production of epoxy resins used in the manufacture of plastics with special applications, such as the barrels of grenade launchers.

EVIDENCE FOR WORK-RELATED ASTHMA

There is only one study in which asthmatic workers have undergone specific bronchial challenge, and this was with a mixture of MTHPA and hexahydrophthalic anhydride (HHPA), because there was occupational exposure to both (Drexler *et al*., 1994). Fourteen out of an exposed work-force of 110 reported exposure-related asthmatic symptoms, and 8 of these underwent apparently open simulated occupational challenge, without control substances. Irritant effects were apparently assessed by an independent observer being present in the chamber at the time of challenge, although the results were not reported. Two of the eight subjects responded with asthmatic reactions (increases in airway responsiveness) and a further 4 with rhinitis. Overall, the study indicates that the two anhydrides MTHPA and HHPA can together induce work-related respiratory symptoms in a proportion of exposed workers, but it is not possible to conclude anything about MTHPA alone.

A group of workers, 13 with nasal symptoms and 7 without, who had been exposed to relatively high levels of MTHPA (0.020 - 0.150 mg/m^3) took part in a nasal challenge study (Nielsen *et al*., 1994). Control subjects were not included, nor were the challenges performed blinded or interspersed with saline. Specific immunoglobulin E (IgE) was also measured. Individual results were not given, but it was clear that positive nasal challenge responses occurred primarily in individuals who had nasal symptoms and specific IgE to MTHPA. Those who did not have specific IgE, with or without symptoms, reacted less or not at all at nasal challenge, suggesting that the nasal response at challenge may have been immunologically mediated.

Asthmatic symptoms associated with exposure to MTHPA have also been reported where challenges have not been performed (Nielsen *et al*., 1989; Nielsen *et al*., 1992; Tarvainen *et al*., 1995). One of these reports included a follow-up study (Nielsen *et al*., 1992). Some workers who had left employment up to 5 years before apparently still reported ocular and upper airway symptoms as well as asthma, whereas for others removal from exposure for 3 months led to a complete disappearance of symptoms and improvement in non-specific bronchial hyper-responsiveness. Furthermore, for one group as a whole, decreasing the exposure level to one tenth of the previous concentration for three months did not lead to an improvement in either symptoms or non-specific bronchial hyperresponsiveness. The relative severity of the symptoms experienced while at work was unclear.

SUPPORTING DATA

A series of linked reports have investigated the immunological profile of workers exposed to MTHPA. One man who developed asthma associated with exposure to only MTHPA had specific IgE, but not specific IgG, to an MTHPA-human serum albumin conjugate, raised total IgE, and a positive skin prick reaction to the conjugate (Nielsen *et al*., 1989).

Current (144) and former (26) workers from the same factory were subsequently studied and the results presented in a comprehensive but not entirely consistent report (Nielsen *et al*., 1992). Individuals were given skin prick tests, and their sera examined for specific IgE and IgG to an MTHPA-human serum albumin conjugate. About 15% of current workers were skin-prick positive and about 20% had specific IgE; the incidence was lower in those who had left their jobs for up to 5 years (10% and 8% respectively), which would be expected since specific IgE levels dropped with a half-life of one year after cessation of exposure to another anhydride (Venables *et al*., 1987). Specific IgG was found most often in the highest exposure group (24%), occasionally in others (5%) and not at all in those who had left employment. All specific IgG positive sera were also positive for specific IgG_4 (Welinder *et al*., 1990). Unexposed control subjects were negative for all 3 tests. Further subdivision of the groups according to exposure level revealed that both specific IgE and positive skin prick tests were more prevalent in those exposed to higher concentrations (Welinder *et al*., 1990). However, there was little correlation between clinical symptoms and the presence of specific IgE or IgG (Nielsen *et al*., 1992). In a proportion of the subjects investigated further, there was a positive correlation between the presence of specific IgE, but not symptoms, and the ability to respond to nasal challenge with MTHPA (Nielsen *et al*., 1994).

A woman developed contact urticaria, rhinitis, cough and bronchial hyperresponsivenss to histamine in association with the use of MTHPA and a polyester resin that contained a low concentration of phthalic anhydride (Tarvainen *et al*., 1995). She had increased total IgE and high specific IgE to both anhydrides conjugated to human serum albumin, with a lesser reaction to the resin. Inhibition tests indicated strong cross-reactivity amongst the anhydrides and with the resin. After undergoing skin prick testing, which proved positive for the anhydrides and the resin, she developed an urticarial and asthmatic reaction.

Specific IgE and skin prick reactions were measured for human serum albumin conjugates of MTHPA, HHPA and phthalic anhydride in 109 workers exposed to MTHPA and HHPA (Drexler *et al*., 1994). Not all staff were tested with all anhydrides. There was cross-reactivity between all three anhydrides. In summary, 20 (18%) of workers had positive skin prick tests or specific IgE that reacted with at least one anhydride, but there was poor correlation between these results and work-related symptoms.

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C19: PAPAIN

SUMMARY AND CONCLUSION

Several reports demonstrate that exposure to papain in the workplace can lead to the development of occupational asthma in a substantial proportion of workers. There are also positive findings in a number of bronchial challenge tests. In workers with symptoms, the results of assays of specific immunoglobulin E (IgE) and skin prick tests indicate an immunological response to papain. Occurrence of blood-stained nasal secretions in workers exposed to high levels of papain could reflect the proteolytic activity of the enzyme.

There is sufficient evidence to conclude that papain meets the revised EU criteria (1996) for classification as a respiratory sensitiser (a cause of asthma) and labelling with R42.

INTRODUCTION

Papain is a sulphydryl protease derived from latex of the fruit of the paw-paw tree, *Carica papaya*. Its molecular weight is 23 000 daltons. The highly potent and broad based proteolytic activity of papain has led to its use for meat tenderising, clearing of beer, treatment of wool and silk and as an ingredient in food, cosmetic and pharmaceutical products.

EVIDENCE FOR WORK-RELATED ASTHMA

Several reports have suggested a link between occupational exposure to papain and development of asthma. Two of these reports provide further evidence for this association from bronchial challenge or lung function tests.

Baur *et al* (1982) studied 33 workers exposed to papain and found a positive correlation between eye, nose and respiratory symptoms and estimated level of exposure. Fifteen workers displayed symptoms of asthma. Individuals in the high exposure group regularly developed a blood-stained nasal secretion lasting up to 24 hours after exposure. The length of exposure prior to development of symptoms ranged from several days to 8 years. Bronchial challenge tests with 0.001-0.5mg papain were clearly positive in 8/9 symptomatic subjects with immunological evidence for papain sensitisation. The reaction was immediate in 5 cases and dual or prolonged in 3 cases. Negative results following inhalation of 0.5mg of papain were obtained in 3 non-exposed asthmatic control subjects, but further evidence that the tests were fully controlled and conducted in a blinded fashion was lacking.

In a study of 23 workers regularly exposed to papain as a major active ingredient in a pharmaceutical product, 12 subjects displayed moderate-severe pulmonary symptoms following several weeks or months of eye and nasal complaints. Pulmonary symptoms developed within minutes up to one hour after entering the workplace, or later following several hours of exposure (Novey *et al*., 1980). The late type continued after work, often producing nocturnal wheezing dyspnoea. The greatest frequency and severity of pulmonary symptoms was seen in those with the highest level of exposure (determined arbitrarily). Five subjects who were atopic, giving positive findings in a test for common allergens, developed pulmonary symptoms sooner than non-atopic individuals. Pulmonary function tests performed in 17 workers, before and 5 minutes after inhalation of 1.3mg of metaproterenol sulphate, were significantly different from predicted values. As most workers smoked the results were compared between those with and those without an immunological response to papain, based on specific IgE levels (smoking status was similar in both groups). Those in the former group generally showed reduced expiratory flow rates and a larger improvement in expiratory flow rates after use of a bronchodilator. The 12 workers with pulmonary symptoms were relocated, and the 5 of this group who were interviewed 4-11 months later were found to be asymptomatic.

Garmendia Goitia and Joral (1992) studied 19 workers exposed to papain for 3 months every year in a pharmaceutical company. Six subjects reported symptoms of rhinitis and bronchial asthma during exposure, but were asymptomatic during the rest of the year. The first symptoms appeared between 3 and 12 years after initial exposure to papain. Tests of respiratory function produced normal values but were conducted when subjects were not working with the enzyme.

SUPPORTING DATA

The presence of raised levels of papain-specific IgE in workers exposed to papain has been demonstrated in several studies (Novey *et al*., 1980; Baur *et al*., 1982; Baur *et al*., 1988; Garmendia Goitia and Joral, 1992). Results from some of these studies suggest that specific IgE occurs with greater frequency in exposed workers with pulmonary symptoms compared with asymptomatic exposed workers. In a study of 31 workers, 1/4 subjects considered to be exposed to the highest levels of papain and displaying respiratory symptoms, was positive for papain-specific IgE and 4/4 were positive for papain-specific IgG (Vogelmeier *et al*., 1985). Ten out of 13 symptomatic workers with low-moderate exposure demonstrated positive results for IgE and IgG. All controls and, with the exception of 2 subjects, all asymptomatic workers, were negative for specific IgE and IgG.

Positive skin prick tests have been demonstrated in a number of workers, particularly symptomatic individuals, exposed to papain (Baur *et al*., 1982; Garmendia Goitia and Joral, 1992; Losada Cosmes, 1991).

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C20: PENICILLINS

SUMMARY AND CONCLUSION

A number of reports indicate that workers who have been exposed to penicillins have developed asthma. The findings of bronchial challenge tests conducted in some subjects demonstrate that penicillins such as ampicillin can cause a delayed asthmatic reaction. Results from skin tests lack clarity and in the absence of other data, the mechanism by which penicillins may produce an asthmatic response is unclear.

There is sufficient evidence to conclude that penicillins meet the revised EU criteria (1996) for classification as respiratory sensitisers (causes of asthma) and labelling with R42.

INTRODUCTION

The penicillins form a large group of natural or semisynthetic antibacterial antibiotics derived directly or indirectly from the fungus *Penicillium*. They exert their effect by interfering with the final stage of the synthesis of a component of the bacterial cell wall. Right from their introduction into therapeutic use the penicillins became associated with contact dermatitis and other allergic reactions, and topical application was discontinued. Ampicillin is the most widely used semisynthetic penicillin.

EVIDENCE FOR WORK-RELATED ASTHMA

Anaphylactic reactions to penicillins were reported soon after their introduction, and asthma became recognised as part of the anaphylactic response to systemic administration. However, it was over 20 years before cases of occupational asthma related to penicillin exposure were clearly documented in the open literature (Montanaro, 1992).

Four workers employed in a factory producing penicillin and a number of semisynthetic antibiotics were studied by Davies *et al* (1974). Three developed asthma and rhinitis 2 years after starting work with these materials. The fourth subject developed shortness of breath and productive cough after 4 years. Bronchial challenge testing was carried out in a single-blinded manner using ampicillin and, in 3 subjects, with benzyl penicillin. Lactose was used as a vehicle and as a negative control substance. Late and generally marked asthmatic reactions were demonstrated in each asthmatic worker after challenge with the penicillins. The fourth individual showed no response and was subsequently diagnosed with chronic obstructive bronchitis.

Wuthrich and Hartmann (1982) have described the case of a factory worker who developed respiratory difficulties whilst employed in a production facility where tetracyclines, chloramphenicol and ampicillin were formulated. When the subject discontinued work, slow recovery occurred. Within 2 weeks of resuming duties, considerable worsening of respiratory problems was observed. A bronchial challenge test was conducted using lactose, tetracycline, ampicillin and chloramphenicol given in an order which was unknown to the patient. Four hours after inhalation of ampicillin, the forced expiratory volume in one second dropped by 42%. It was claimed by the authors that the data indicated a delayed asthmatic response to ampicillin. However, the information given in the report does not clearly exclude an effect with tetracycline, chloramphenicol, or even lactose.

In a Danish study, 45 workers in a factory producing the semisynthetic penicillins pivmecillinam and pivampicillin developed dermatitis, of which 19 also showed allergic symptoms of the eyes, nose or lungs indicative of hayfever (17 cases) and/or asthma in 5 cases (Moller *et al*., 1986). The duration of exposure before these symptoms arose was short, often only weeks and in all cases within 5 months. The asthma attacks found in these cases were often of the delayed type, starting 5-6 hours after the exposure that provoked them. A follow-up study revealed further information regarding the progress of this outbreak, briefly reporting on the 56 cases of allergy

recorded during 15 years of production of pivampicillin (Moller *et al*., 1990). Of these 56, 11 developed asthma, 31 hay fever and 50 allergic dermatitis on the face and arms. No further useful information was given.

The prevalence of allergic disease of the respiratory tract and skin among Russian workers engaged in the production of ampicillin trihydrate and ampicillin sodium salt has been investigated (Karpenko, 1986). The actual number of workers evaluated is not known. Antibiotic concentration in the air varied with stage of production. Overall, there was an apparent association between airborne levels and occurrence of respiratory disease, with 80% prevalence at the highest level of exposure and 12% where exposure was lowest.

A review indicates that during the 1960s there were sporadic cases of occupational asthma among health professionals (particularly doctors, midwives and nurses) that were related to their preparation of penicillin for injection, when the antibiotic was handled in powdered form, and their administration of aerosols of the drug (Rosenberg and Gervais, 1991). The use of greater precautions now apparently prevents this sort of occupational asthma.

Little further useful information is available. One of 17 confirmed cases of occupational asthma in Singapore was ascribed to ampicillin exposure at a pharmaceutical facility (Lee and Phoon, 1989). No further details are available as only a summary of the report could be obtained. A study of 331 workers in a Polish penicillin factory found one with bronchial asthma alongside 79 with allergic dermatitis and 6 with urticaria (Rudzki *et al*., 1965). Similarly, a study of 169 workers involved in the manufacture of synthetic penicillins in an American factory found 2 that complained of wheezing, 27 with rhinorrhea and/or sneezing, 14 with itching eyes and 37 with localised rash (Shmunes *et al*., 1976).

SUPPORTING DATA

Skin prick tests using ampicillin were negative in 3 workers with a positive inhalation challenge to this antibiotic (Davies *et al*., 1974). The same subjects also showed an increase in blood eosinophil counts, 24 hours after the asthmatic reaction. Skin tests with ampicillin were negative for a worker experiencing respiratory difficulties following exposure to this and other antibiotics (Wuthrich and Hartmann, 1982). The serum immunoglobulin E level in this subject was high.

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C21: PERSULPHATES

SUMMARY AND CONCLUSION

A number of well-conducted studies provide evidence that persulphate salts can induce asthma in the workplace. In several cases specific reactions have been obtained at bronchial challenge under conditions which do not produce a response in normal or previously non-exposed asthmatic subjects. These studies are backed up by case reports of occupational asthma associated with persulphate use. While most people with persulphate asthma have given positive responses in skin prick tests, this may be because of direct histamine release rather than an immunologically-mediated reaction. Other immunological data are scarce and inconclusive.

There is sufficient evidence to conclude that persulphate salts meet the revised EU criteria (1996) for classification as respiratory sensitisers (causes of asthma) and labelling with R42.

INTRODUCTION

Persulphate salts (ammonium, potassium and sodium) are strong oxidising agents with wide industrial use. They are also used to enhance the action of peroxide hair bleaches, for which they are supplied as a powder to mix with liquid peroxide shortly before use. Persulphate hair bleaches have produced both irritant and allergic contact dermatitis, as well as urticarial and respiratory reactions (Fisher and Dooms-Goossens, 1976; Kellett and Beck, 1985; Kleinhans and Ranneberg, 1989). The contact urticaria is not immunologically-mediated, but thought to be due to the fact that persulphate is a weak histamine-releasing agent (Calnan and Schuster, 1963; Parsons *et al*., 1979). It is not known why only some individuals are sensitive to this action.

EVIDENCE FOR WORK-RELATED ASTHMA

There have been a number of well-conducted studies of hairdressers with work-related asthmatic symptoms that have included specific bronchial challenge tests, performed blinded, using hair bleach or persulphate, either as powder or aerosolised solution. In some studies, controls who were either non-asthmatic, or asthmatic with hyperresponsive airways, were also challenged; none gave positive reactions.

Of 12 ‘tinters’ from a hairdressing salon who used persulphate-containing bleach, 4 had work-related asthmatic and nasal symptoms, which had developed after a latent period of at least six months (Blainey *et al*., 1986). An affected individual from another salon was also included for investigation. All 5 were hyperresponsive to histamine, though other lung function parameters were normal. Only those with symptoms reacted at specific challenge, giving late asthmatic responses, and controls (including asthmatics) failed to react. All 4 of the subjects who also underwent nasal challenge gave positive reactions.

Agustin *et al*., (1992) reported the cases of two hairdressers who developed work-related rhinitis, conjunctivitis and, in one case, asthma, several years after first using bleaching powders. Both had normal respiratory function, but the asthmatic subject was hyperresponsive to methacholine. At specific bronchial challenge, the person with asthma developed a late response, while the other suffered immediate severe nasal symptoms.

A young woman developed work-related respiratory symptoms about a year after starting work in a hairdressing salon (Parra *et al*., 1992). When she was investigated, after a month’s absence from work, she was hyperresponsive to methacholine. On specific bronchial challenge, she developed a late, prolonged reaction followed by recurrent nocturnal falls in forced expiratory volume in one second, for 96 hours after the test.

Another case of work-related asthma, with associated sneezing and rhinoconjunctivitis, has been described, in which a young woman worked for 3 years before developing symptoms (Pankow *et*

al., 1989). As in other cases, lung function was normal but the airways showed non-specific hyperresponsiveness. On unblinded bronchial challenge, she suffered an immediate asthmatic attack. Normal and asthmatic controls did not react.

A beautician with a history of mild seasonal rhinitis developed work-related asthma (Schwartz, 1989). Lung function was normal, and she was not hyperresponsive to methacholine. She underwent blinded bronchial challenges with a number of hair care preparations, and reacted only to a persulphate-containing bleach with an immediate reaction (it was unclear for how long measurements were continued). The patient declined challenge with persulphate itself.

All of these well-conducted studies provide evidence that persulphate salts are capable of inducing asthma and can cause specific reactions at bronchial challenge under conditions which do not induce a response in normal or previously non-exposed asthmatic people.

These studies are backed up by several case reports of occupational asthma associated with persulphate use, in which the bronchial challenge tests performed were not blinded and omitted controls. These include two cases, both positive at challenge (Pepys *et al*., 1976); 5 cases, 4 challenged - 2 positive, 1 negative, 1 equivocal (Therond *et al*., 1989); one case, positive (Gamboa *et al*., 1989); one case, positive (Schwaiblmair *et al*., 1990); three cases, one challenged - positive (Wallenstein *et al*., 1993).

There are also reports of persulphate effects in occupations other than hairdressing. One concerns an Italian factory that used ammonium and potassium persulphate during the manufacture of hydrogen peroxide, in which 12% of the workers suffered from asthma that usually developed within 6 months of starting work (Barsotti *et al*., 1951). Bronchial challenges were performed with an aerosol of a 1% ammonium persulphate solution; affected workers, but not controls, responded positively to challenge. In another study, 2 chemical factory workers who bagged persulphates developed work-related nasal and asthmatic symptoms within a few weeks of beginning work (Baur *et al*., 1979). Neither underwent bronchial challenge, and symptoms resolved on avoiding exposure.

SUPPORTING DATA

Skin prick tests, and occasionally intradermal or scratch tests, have been performed on many of the people reported as having persulphate-related asthma or rhinitis. Either persulphate or bleach powder solutions have been used; negative controls have sometimes been included. The tests have been positive in most of those studied (Gaultier *et al*., 1966; Blandin, 1970; Fisher and Dooms-Goossens, 1976; Pepys *et al*., 1976; Baur *et al*., 1979; Blainey *et al*., 1986; Pankow *et al*., 1989; Agustin *et al*., 1992; Escudero Pastor *et al*., 1992; Parra *et al*., 1992; Wallenstein *et al*., 1993). There have also been some negative results reported (Baur *et al*., 1979; Blainey *et al*., 1986; Gamboa *et al*., 1989; Agustin *et al*., 1992; Wallenstein *et al*., 1993). In one study, the results of intradermal tests in 3 people correlated with bronchial challenge data (Wallenstein *et al*., 1993). Amongst employees manufacturing persulphates, work-related breathing difficulties were found more often (6/8) in those who were positive than in those who were negative (9/44) in skin prick tests (Wrbitzky *et al*., 1995). In an early study, a scratch test that was strongly positive triggered within minutes a “violent” attack of asthma (Blandin, 1970). While most people with persulphate asthma have given positive skin prick tests, this may be because of direct histamine release rather than an immunologically-mediated reaction.

In hairdressers with asthma, total immunoglobulin E (IgE) levels have generally been normal, though increased in two people, and decreased after avoidance of exposure in another (Gamboa *et al*., 1989; Pankow *et al*., 1989; Schwaiblmair *et al*., 1990; Agustin *et al*., 1992; Parra *et al*., 1992). No specific IgE to persulphates has been found in three separate cases tested (Gamboa *et al*., 1989; Schwaiblmair *et al*., 1990; Parra *et al*., 1992). However, the serum from an asthmatic patient was positive for both hair bleach and sodium persulphate in a Prausnitz-Kustner test for

passive transfer of specific IgE (Escudero Pastor *et al*., 1992). Overall, these immunological data are scarce and inconclusive.

In peripheral blood studies, one person had eosinophilia, and another developed neutrophilia and eosinophilia following positive bronchial challenge (Schwaiblmair *et al*., 1990; Parra *et al*., 1992).

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C22: PHTHALIC ANHYDRIDE

SUMMARY AND CONCLUSION

The results of chemical factory health surveys in several countries provide convincing evidence that phthalic anhydride can cause asthma and rhinitis in a proportion of exposed individuals. This conclusion is backed up by occasional reports of phthalic anhydride-associated asthma in earlier literature and a number of recent case reports. Some positive bronchial challenge test results are also available. Immunological data are too limited to allow firm conclusions to be made regarding mechanism of action.

There is sufficient evidence to conclude that phthalic anhydride meets the revised EU criteria (1996) for classification as a respiratory sensitiser (a cause of asthma) and labelling with R42.

INTRODUCTION

Phthalic anhydride is a versatile chemical intermediate which has applications in the manufacture of a wide range of commercial products, including plasticisers, resins, dyes, pesticides and pharmaceuticals.

The following information has been summarised from an HSE Criteria Document for an Occupational Exposure Limit, where a more detailed critical appraisal of the available data can be found (Ridgway *et al*., 1996).

EVIDENCE FOR WORK-RELATED ASTHMA

Detailed studies of asthma and other respiratory effects related to phthalic anhydride exposure has been conducted in several Swedish polyester factories (Wernfors *et al*., 1986). “Phthalic anhydride asthma”, defined as the occurrence of asthmatic symptoms during employment at the plant with an unequivocal and plausible relationship to phthalic anhydride exposure, was diagnosed at two plants. It was reported for 12% (6/48) of current and 21% (15/70) of former employees. Asthma started only during periods of high exposure, but could then persist at low exposure levels. In approximately half the cases, asthma was preceded by a period of rhinitis. Rhinitis was also experienced by 19% of the non-asthmatic workers. The latent period between the start of employment and onset of asthma ranged from one month to 16 years, with about a third of cases appearing within a couple of months or less. Two asthmatics received bronchial challenge tests with phthalic anhydride, and these were positive. A subsequent study confirmed the presence of phthalic qanhydride-associated asthma in Swedish polyester resin factories (Nielsen *et al*., 1988). Phthalic anhydride-associated asthma has also been reported in a study conducted at a Finnish phthalic anhydride manufacturing plant (Ahlberg and Keskinen, 1984).

In a study conducted at two factories in China where phthalic anhydride was produced and used to manufacture dioctylphthalate, twenty-one phthalic anhydride workers, with an average duration of exposure of about 8 years. were examined (Liu *et al*., 1985). Ten had asthmatic symptoms associated with phthalic anhydride exposure. The first signs of asthma were noted at between 6 months and 17 years after initial exposure, and the asthma was invariably associated with rhinitis and conjunctivitis. The non-asthmatics showed signs of slight rhinitis and tracheitis after contact with phthalic anhydride.

There are also a number of earlier workplace surveys, as well as various case reports, of asthma associated with phthalic anhydride exposure. For several of the cases, well-conducted bronchial challenge tests provide clear evidence that phthalic anhydride was the causative agent.

SUPPORTING DATA

Some immunological data were available from the workplace health surveys. Phthalic anhydride specific immunoglobulin E (IgE) or IgG levels were elevated in some asthmatic workers, but the data were too limited to allow firm conclusions to be drawn about the role of the immune system in inducing the respiratory response.

No internationally-validated animal tests are currently available that allow prediction of the ability of a chemical to induce asthma in man. However, evidence that phthalic anhydride has the potential to cause respiratory hypersensitivity, associated with the presence of specific IgG and IgG_1 antibodies, has been obtained in guinea pigs (Sarlo and Clarke, 1992).

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C23: PIPERAZINE

SUMMARY AND CONCLUSION

The use of piperazine has been associated with the development of asthma in the workplace, and some limited positive bronchial challenge data are available. The finding that specific immunoglobulin E (IgE) has been found in about half of those with symptoms, but rarely occurs in exposed, asymptomatic individuals, suggests an immunological basis for the asthma.

There is sufficient evidence to conclude that piperazine meets the revised EU criteria (1996) for classification as a respiratory sensitiser (a cause of asthma) and labelling with R42.

INTRODUCTION

Piperazine, also called diethylenediamine, is used medically as an anti-helminthic agent. Industrially, it is handled in the anhydrous form or as the hexahydrate, both being transparent, crystalline solids that are very water soluble. Anhydrous piperazine is reported to be a skin and eye irritant, while no data are available for the hexahydrate (Sax and Lewis, 1989).

EVIDENCE FOR WORK-RELATED ASTHMA

Industrial use of piperazine has been associated with the development of occupational asthma (determined by questionnaire or medical records), in particular with the flaking of dusty anhydrous piperazine (Hagmar *et al*., 1982). The flaking of the less dusty hexahydrate brought on attacks in previously affected individuals. The latent period before development of asthma was less than one year in 9/15 cases, and length of employment was significantly associated with the occurrence of asthmatic symptoms (Hagmar *et al*., 1982; Hagmar *et al*., 1984). Amongst 131 current workers, 7% had asthma attributed to piperazine, whereas for current and former workers combined 15-19% had various asthmatic symptoms. This suggested a higher prevalence amongst former workers, although a later study of the same, current, workforce estimated the prevalence of asthma to be 11% (Hagmar and Welinder, 1986).

Two industrial chemists developed rhinitis, progressing to asthma attacks, that was associated with using piperazine (Pepys *et al*., 1972). Neither subject was atopic, and both underwent bronchial challenge tests (probably blinded) with lactose and a range of concentrations of up to 50% piperazine dihydrochloride in lactose. The top dose was also tested with and without cromoglycate in a blinded manner. The findings for two normal and one asthmatic control subjects were not reported but are presumed to be negative. Both patients reacted only to the higher concentrations (25-50%) of piperazine, giving 20-50% drops in forced expiratory volume in one second. These reactions were prevented by cromoglycate but not placebo. Nasal challenge tests with piperazine solution were negative.

There are a further two reports describing bronchial challenges conducted with piperazine. In the first, a worker reacted with a dual response to 50 mg piperazine but not to lower concentrations or saline; 2 asymptomatic controls failed to respond (Hagmar *et al*., 1982). In an earlier, poorly-reported study, a man who underwent bronchial challenge with piperazine hexahydrate experienced a late asthmatic response, but no control challenges were carried out (McCullagh 1968).

SUPPORTING DATA

Raised specific IgE to a piperazine-human serum albumin conjugate has been found in two workers with piperazine-related occupational asthma (Welinder *et al*., 1986). In a workforce study, 5 of 72 workers exposed to piperazine had raised specific IgE to this conjugate (Hagmar and Welinder, 1986). Four of the 5 had occupational asthma, but so did 4 of the remaining 67 without specific IgE. Only one subject had raised specific IgE but no history of asthma. Only 2 of the 5

skin prick tests reported were positive (Hagmar *et al*., 1972; Pepys *et al*., 1972; Welinder *et al*., 1986).

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C24: SOME REACTIVE DYES

SUMMARY AND CONCLUSION

A number of reports indicate that workers who have been exposed to reactive dyes can develop asthma. Although the available bronchial challenge data have not been generated under the most stringent conditions, they do suggest that the asthma is induced by a specific mechanism. There is evidence for an immune response occurring in workers with symptoms, specific immunoglobulin E (IgE) in particular showing a good correlation with bronchial challenge response. Surveys indicate that the prevalence of occupational asthma amongst current workers is 4%, with the suggestion of a higher incidence in leavers. It should be noted that the term "reactive dye" covers a range of chemical classes, and not all may be responsible for causing occupational asthma.

There is sufficient evidence to conclude that some reactive dyes meet the revised EU criteria (1996) for classification as respiratory sensitisers (causes of asthma) and labelling with R42.

INTRODUCTION

Reactive dyes have become used widely since their introduction in 1956. Each dye is made up of 3 moieties; the chromophore (dye), hydrophilic groups to improve water solubility, and a reactive group that will react directly with the substrate, usually a protein or cellulose fibre. The chemical class of the chromophore can be azo, anthraquinone, phthalocyanine or oxazine. The reactive groups in use include vinylsulphonyl, halogenated triazinyl, bromoacrylamide, halogenated pyrimidine and pyrazolone. When the dyes are supplied, they contain (unspecified) additives (Stern, 1985; Luczynska and Topping, 1986; Wattie, 1987; Rosenberg *et al*., 1988; Romano *et al*., 1992).

EVIDENCE FOR WORK-RELATED ASTHMA

There are a large number of reports indicating that workers who have been exposed to reactive dyes may develop work-related asthma. The wide range of reactive dyes implicated in asthmatic reactions indicates that no one type of chemical class or reactive group is responsible. Conversely, there is no evidence to suggest that all reactive dyes are implicated, therefore some may not be involved. In some of the studies, people with nasal and/or respiratory symptoms, associated with working with reactive dyes, have undergone bronchial challenge with the dyes. Although none of the challenges have been performed in a blinded manner, some studies have involved workers being challenged with 2 or 3 different dyestuffs, but only reacting to one, indicating a specificity of reaction. There are no reports of normal subjects being challenged in control tests.

A man developed work-related asthma and urticaria, starting 15 months after he began to handle dyes (Romano *et al*., 1992). He continued to work, using a respirator, and was studied about 2 years later. He did not show hyper-responsiveness to methacholine before or after bronchial challenges, which were performed with dye powders to which he was occupationally exposed. Exposure to a mixture of 2 related dyes, or to a lactose control, for 30 minutes failed to produce any bronchial reactions, whereas exposure to one other reactive dye for only 4 minutes induced an immediate drop of 49% in the forced expiratory volume in one second, and an anaphylactic response requiring treatment.

Four men occupationally exposed to powdered reactive dyes developed work-related rhinitis then asthma with a latent period of 6 months to 4 years (Alanko *et al*., 1978). None had pre-existing asthma, though one was atopic. Three had bronchial hyperresponsiveness to histamine (the fourth man had not been exposed to dyes for several months at the time of this test). On simulated occupational challenge, involving the use of different dyes for different people, all

developed immediate reactions. All also gave positive nasal challenges. Two men were also challenged with a second dye, but did not react, and there were no reactions to lactose powder.

Ringenbach (1985) briefly described the case of one woman who worked dyeing yarns, and had an 8-year history of asthmatic symptoms, though she did not report these as work-related. Two years before the study she had marked bronchial hyperresponsiveness to a choline derivative. At the time of study, when she had not been exposed for several months, she was challenged with 5 dyes that she had previously used; she reacted to two (one immediate and one late reaction) but not to the others. No further details were given. The report also gave brief details of 3 people with circumstantial evidence of asthma due to handling reactive dyes, but in whom bronchial challenges were not performed.

Three patients suffering from occupational asthma and/or rhinitis were described who had used reactive dyes in powder form and had been heavily exposed to dye dusts over a period of years (Estlander, 1988). They underwent nasal and bronchial challenges with dyes to which they had been occupationally exposed, two reacting positively to bronchial challenge and one to nasal challenge. Placebo challenges were performed, but no details were given.

Park and colleagues studied 9 men who complained of work - related asthma, having been exposed to dyes for 6-25 months (Park *et al*., 1989). Eight had airways that were hyper-responsive to methacholine, and 3 were atopic. Known concentrations of dye solutions were nebulised and bronchial challenges performed; a saline control was included but the tests were not blinded. All 9 men gave positive reactions that consisted of 4 early and 5 dual responses. Three further dye-workers, all without non-specific bronchial hyperresponsiveness and only one of whom reported work-related asthma, were challenged under the same conditions with one particular dye; all three responded positively with early responses (Park *et al*., 1990).

In an investigation for which only brief details were provided, a worker with a history of occupational asthma gave a positive response on bronchial challenge with one of the dyestuffs that he used (Stern, 1985; Docker *et al*., 1987; Wattie, 1987). Although this dyestuff was subsequently removed from his workplace, he later died of asthma at work. Of the nine other workers from the same dyeworks, two had a history of occupational asthma, and challenge induced a bronchial response and rhinitis in both, and in one also produced conjunctivitis and mild urticaria.

There are two surveys available in which the prevalence of reactive dye-related occupational asthma has been investigated with the aid of bronchial challenge testing. These tests were performed in an unblinded fashion and without placebo controls. As in the above studies, workers were exposed to numerous reactive dyes, but patient reaction was assessed to only a few; thus the incidence of positive reactions may be an underestimate.

A survey was made of the 309 employees in a Korean dye company that used a range of reactive dyes (Park *et al*., 1991 a). Although different occupations were mentioned (there were 271 dye processors, 31 laboratory workers and 7 office staff), the results were expressed only as a proportion of the total workforce. Seventy-eight (25%) of the employees reported lower respiratory tract symptoms, with or without nasal or eye symptoms, that were related to dye exposure. A further 26 (8%) had nasal symptoms only. Thirty-eight of the 78 were hyperresponsive to methacholine, including 20 who were considered to be within the asthmatic range. These 20 underwent specific bronchial challenge testing with a nebulised solution of a dye to which they were occupationally exposed. Thirteen gave positive reactions consisting of 6 early, 1 late and 6 dual responses. The lack of response in seven subjects suggests that a non-specific irritant action was not involved. The data indicated an overall prevalence of occupational asthma with positive bronchial challenge of approximately 4%. A neighbouring reactive dye factory was also studied; 11/81 employees (14%) had symptoms of occupational asthma (Park *et al*., 1991b). Poor reporting made it impossible to determine the number of positive bronchial challenge tests.

A study was carried out amongst 106 textile dye workers in Czechoslovakia (Kalas and Runstukova, 1980). The average age of the workers was 28 years and they had been exposed to reactive dye (ostazine and procion) dusts for a mean period of 9 years. Eight workers (7%) had symptoms suggestive of work-related asthma, while a further 22 had other work-related allergic symptoms, such as rhinitis and conjunctivitis. There were indications that a "survivor effect" was occurring within the workforce; 42% of employees left the factories within 5 years, with indications that this was due to the development of "sensitization". On specific bronchial challenge with dye powder at about one tenth of the dust concentration in the workplace, 4 cases (3.8%) reacted with "typical asthmatic responses", 2 being late responses. In addition, 26 workers had a "bronchospastic reaction" at challenge; the nature of this response was not clarified and was of uncertain significance. This study indicated that the prevalence of confirmed occupational asthma in those currently employed in the dye works was 4%, a figure in agreement with that reported above.

In addition, there are several reports available in which respiratory symptoms related to dye exposure have been noted in workers, but specific bronchial challenges have not been performed (Hagmar *et al*., 1986; Luczynska and Topping, 1986; Thoren *et al*., 1986; Docker *et al*., 1987; Estlander, 1988; Topping *et al*., 1989; Wass *et al*., 1990; Nilsson *et al*., 1993).

SUPPORTING DATA

The immunological responses to reactive dyes in exposed people have been widely studied (Alanko *et al*., 1978; Hagmar *et al*., 1986; Luczynska and Topping, 1986; Thoren *et al*., 1986; Docker *et al*., 1987; Estlander, 1988; Park *et al*., 1989; Topping *et al*., 1989; Park *et al*., 1990; Wass *et al*., 1990; Park *et al*., 1991a; Park *et al*., 1991b; Park and Hong, 1991; Romano *et al*., 1992; Nilsson *et al*., 1993).

Total serum IgE levels have been found to be raised in about 50% of those exposed to dyes, whether or not they have symptoms. The presence of specific IgE to dye-human serum albumin conjugates has generally been found more often in symptomatic (30-100%) than in asymptomatic, exposed workers (0-13%). Although unexposed people do not have specific IgE, there is conflicting evidence as to whether or not the occurrence of specific IgE is dependent on the level of exposure. The presence of specific IgG seems to correlate with exposure, and that of specific IgG_4 with either symptoms or the presence of specific IgE. The few studies which compared bronchial challenge results and specific IgE have found a good positive correlation between the two. Scratch/prick tests with free or conjugated dyes have been performed, and have showed an apparent correlation between a positive result and symptoms, but the association with challenge or specific IgE has been very variable, and no conclusions can be drawn.

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C25: ROSIN-BASED SOLDER FLUX FUME

SUMMARY AND CONCLUSION

A detailed study carried out in the 1970s among workers at an electronics factory in the UK, and several case reports, indicate that occupational asthma can be a significant health problem among solderers exposed to rosin-based solder flux fume. Considering the workers reported with asthma, the available medical and work histories, and diagnostic bronchial challenge test data, provide evidence for a specific respiratory response in some cases. There are, however, also a number of small-scale epidemiological studies which have yielded essentially negative findings and, given the ubiquitous presence of components of rosin in the environment, there must remain a question as to whether solder fume actually induced the asthmatic state in affected individuals.

There is sufficient evidence to conclude that rosin-based solder flux fume meets the revised EU criteria (1996) for classification as a respiratory sensitiser (a cause of asthma) and labelling with R42.

INTRODUCTION

Rosins are natural resin derived from pine trees. Most commonly, gum rosin (colophony) is the form used by solderers. The fume produced when soldering with rosin flux consists of two fractions. The particulate fraction is composed of rosin sublimates and thermal decomposition products, which are predominantly a mixture of diterpene resin acids. This fraction makes up approximately 90% by mass of the total fume. The remaining gaseous/vaporous part of the fume is composed of low molecular weight compounds, including acetone, methyl alcohol, aliphatic aldehydes and hydrocarbons.

A potential confounding factor in the assessment of solderers with occupational asthma is possible exposure to toluene diisocyanate, liberated from polyurethane-coated wires during soldering (Burge *et al*., 1979a; Burge *et al*., 1979b). Most of the reports available do not address this issue. However, in their detailed study of an electronics factory in the UK (see below), Burge and co-workers reported that polyurethane-coated wires constituted a small proportion of all wires used and that soldering with them was confined to a few workers. Burge *et al* (1979a) stated that no workers in that factory were found to be sensitive to toluene diisocyanate, although sensitive workers had evidently been seen in other electronics factories.

EVIDENCE FOR WORK-RELATED ASTHMA

Around 1980, reports of a high prevalence of occupational asthma among solderers in the electronics industry led to the conclusion that there was a significant health problem caused by exposure to rosin-based solder flux fume. Burge *et al* (1978) investigated 19 electronics workers who presented with classical symptoms of asthma. Approximately half of them also presented with chest pain, sputum, rhinitis or sore eyes. None of the subjects had chronic bronchitis. These symptoms occurred after many years exposure to undefined concentrations of solder fume and tended to develop within 1 and 4 hours of starting a shift and to persist into the evenings and weekends. Recovery from severe attacks took between 1 and 6 weeks. The median period of work in the factory before symptoms appeared was 6 years. Sick leave due to asthma had been taken by all of the subjects, the majority requiring between 1 and 3 weeks for recovery.

Chest radiographs of the patients indicated that they suffered from no underlying respiratory problems. There were 9 atopics in the group, but no specific antibodies to rosin were found and skin prick tests with rosin gave negative results. In challenge tests, all 19 patients gave a 15% or greater fall in forced expiratory volume in one second (FEV_1) when exposed to solder fume or rosin fume. Controls, including 4 non-exposed asthmatics and 2 healthy workers showed no reactions under comparable conditions. These results suggest the triggering of a respiratory response, but it is not clear if the fume induced the hypersensitive state.

In the same factory, a cross-sectional survey of 446 out of 637 shop floor workers reported combined prevalences of work-related dyspnoea or wheeze or both of 20%, 22% and 6% in solderers, other shop floor workers and controls, respectively (Burge *et al*., 1979b). Impaired lung function (as indicated by significantly decreased FEV_1 and forced vital capacity, FVC) was reported among shop floor workers. Fifty eight of the shop-floor workers with respiratory symptoms were investigated in a small case-control study intended to assess potential aetiological factors other than exposure to solder fume (Burge *et al*., 1979a). Atopy was the most significant factor associated with case status (the incidences of atopy in case and control groups were 40% and 12.5%, respectively). A past history of hay fever, eczema or asthma was weakly but statistically significantly associated with being a case, but a family history of allergic disease and smoking were not. The authors used statistical analysis to conclude that personal factors could have accounted for only 17% of the difference between cases and controls.

In additional electronics factories, Burge *et al* (1980) identified 51 workers with occupational asthma. In bronchial challenge tests, 34 of these subjects responded to rosin-based solder flux fume. Of these, 22 were tested separately with both rosin fume and solder fume, and immediate positive bronchial responses were always observed. Late reactions were uncommon among the responding patients. Exposure times required to elicit a response were generally shorter for rosin fume than solder fume. Negative reactions were observed in 15 patients and equivocal reactions (non-stable control FEV_1 values) in the remaining 2. In subsequent tests, 5 out of 6 responding subjects gave immediate reactions following exposure for 1 to 4 minutes to the fumes of the resin acid, abietic acid.

Twenty three of the responding subjects exhibited bronchial hyperresponsiveness to histamine. Eight of 18 rosin fume-responding patients tested reacted in challenge tests to the amine hydrochloride flux activator. Although exposures to the activator were for a maximum of only 5 minutes, it was reported that a strong unpleasant odour was detectable in these tests and concluded that levels of fume achieved were considerably higher than during regular soldering. Although the underlying mechanism(s) for the responses to flux activator were not identified, liberated hydrogen chloride may have caused primary irritation.

In control tests, 7/15 of the 34 rosin-responsive patients reacted to non-rosin solder flux fume. The study authors noted that reactions to the rosin-free solder were significantly correlated to both histamine responsiveness and reactions to the amine hydrochloride flux activator. As such, this flux may have acted as a non-specific irritant. Up to 1-4 years after the initial investigation of the 51 workers, 28 of the 34 confirmed solder fume-responding asthmatics and 9 of the remainder were followed up to detect residual disability (Burge, 1982b). Asthmatic symptoms among workers in both groups were still present, even in solder fume-sensitive workers who were no longer subjected to occupational exposure.

Burge *et al* (1981) identified 5 cases of work-related wheeze or breathlessness among 45 workers at a rosin-cored solder flux manufacturing plant. Although these individuals were probably all exposed at work to solder fume from rosin flux, no data were available to assess the aetiology of this health problem.

Fawcett *et al* (1976) reported the case of a non-atopic female solderer who developed dry cough and wheeze after 3 years of working with rosin-cored solder flux and liquid resin flux. These symptoms occurred 5 hours into her daily shift and the wheeze persisted into the evenings, with improvement at weekends. Respiratory symptoms were uncommon among the workforce of about 200 shop floor staff. Treatments with bronchodilators and inhaled steroids were ineffective. She gave normal chest X-ray; FEV_1 was 84 % expected and improved after inhalation of salbutamol.

Bronchial challenge tests were conducted in a chamber; it is not clear if they were performed in a blinded manner. Exposure to fume from all of the soldering material produced an immediate reaction, with a 64% fall in FEV_1. The patient was given intravenous aminophylline and FEV_1 recovered within 2 h. However, at 7 h, there was a fall of FEV_1 of 40%. Exposure to rosin-based

solder flux fume caused an immediate reaction only, FEV_1 decreasing by 50% at 15 minutes. This reaction was blocked by inhalation of cromoglycate before exposure. In further tests, the woman responded to rosin fume but not to a control vapour.

Two further cases of solder-related asthma were reported by Fawcett *et al* (1976). Both responded with immediate reactions to rosin-based solder fume in challenge tests. Prior inhalation of cromoglycate, but not a lactose placebo, was effective in blocking this reaction in one of the cases. There was no response to control fume. Both subjects had suffered previously from asthma during childhood, and no definite conclusions can be reached about the underlying mechanisms involved, particularly as no control asthmatics were included in the study.

Four solderers, who suffered from work-related asthmatic symptoms after exposure to rosin-cored solder flux fume for 0.5 - 10 years, were subjected to bronchial challenge tests performed single-blind (*Durham et al*., 1987). Medical histories were not reported, and it is not clear if any of the solderers had underlying states of respiratory illness. The patients were first exposed to solid solder wire (no rosin core) fumes and, in each case, no bronchial reactions occurred. On exposure to rosin-based solder flux fume, 2 of the solderers responded with immediate and late asthmatic reactions, while the other 2 gave early reactions only. No control subjects were included. Overall, the findings implicate the solder fume in the aetiology of the asthmatic symptoms.

Maestrelli *et al* (1985) examined 4 female former solderers who recollected that their asthmatic symptoms first occurred after 2-13 years of soldering with rosin-cored flux. All 4 women showed a non-specific hyperresponsive reaction to methacholine; one of them was atopic and showed elevated serum immunoglobulin E (IgE). They gave significant responses on non-blinded bronchial challenge with rosin-based solder flux or rosin fume, although one woman exhibited nasal irritation to the rosin fume, so that testing was not completed. At a follow-up 2 years later, the women still reported occasional bronchial spasms, and 2 of the women gave immediate responses to rosin fume. No definite responses were seen in the other 2 patients. Three of them were hyperresponsive to methacholine at follow-up, although none responded in further tests to formaldehyde. In these tests, exposure was limited to 10-15 minutes because the patients developed nose, throat and eye irritation. Control, non-exposed, asthmatic subjects (group size not specified) did not respond to solder fume or formaldehyde in comparable challenge tests, even though they showed non-specific bronchial hyperresponsiveness. Overall, the study provides further evidence that exposure to rosin-based solder fume can cause occupational asthma.

Kalas and Runstukova (1982) describe the response to rosin-based solder flux fume of 8 solderers with work-related symptoms of asthma. There were 68 other solderers in the same factory, all of whom were subjectively unaffected by illness. Unfortunately, the nature of previous exposures encountered by the solderers, the challenge tests and the findings amongst the other solderers were not well described, and it is not possible to make any firm conclusions from this study.

Orosz *et al* (1984) reported 2 cases of occupational asthma linked with exposure to rosin-based solder flux fume. Positive reactions were given by both individuals in bronchial challenge tests with rosin fume, while an atopic asthmatic control subject, sensitive to house dust and with no occupational exposure to solder fume, showed no form of airways obstruction when exposed to this fume. Again, however, no firm conclusions can be made from this study, which lacked details of work and medical histories.

A further case was reported by Kovac *et al* (1981). This non-atopic woman developed occupational asthma in her 22nd year working with rosin-cored solder flux. Occupational asthma due to inhalation of solder fume from rosin flux was diagnosed as a result of symptoms reported and decreases in lung function parameters observed in a poorly-reported occupation-type challenge test. No control subjects were exposed, and it is not possible to make any definite conclusions.

During the period 1989 to 1991, a total of 85 cases of asthma attributed by diagnosing physicians to solder/rosin were reported for the UK by the SWORD (Surveillance of work-related and occupational respiratory disease) project (Meredith and McDonald, 1994).

There are also 4 epidemiological studies available that report no clear relationship between work with rosin-cored solder flux and symptoms of asthma. In the first, respiratory symptoms and lung function were investigated in 1611 female electronics workers at 4 company sites (Courtney and Merrett, 1984). This represented 86% of the total female workforce, and no evidence was found to suggest that the group was unrepresentative of the total workforce. Rosin-cored solder was used at this company, but no exposure data were available. Data on respiratory morbidity were collected by a Medical Research Council questionnaire (modified to provide information on hoarseness and running or watering of the eyes and nose), and FVC and FEV_1 were measured at the end of the interview. There were 537 solderers, 246 ex-solderers, 445 non-solderers and 171 office workers studied, and these four groups were subdivided into smokers and non-smokers for statistical analysis of data. Ex-smokers (202 women) and 10 women disabled from working by reasons other than chest or heart disease were excluded. The study was limited to women because the total workforce was predominantly female.

Statistical analysis did not reveal any clear and consistent differences in the prevalence of respiratory or irritative symptoms between the groups. Examination of the medical records of 109 representative ex-solderers from one site did not reveal any women who had changed jobs for medical reasons that were related to soldering.

In the second negative study, health questionnaires were completed by 90% of all solderers at a US electronics factory (Greaves *et al*., 1984). Rosin-cored solder flux was used regularly in this factory by at least 68 of the 104 solderers on the study, but no exposure data were available. The relative risks for wheeze, cough and phlegm were increased on comparison with prevalence rates in the general population, and the respiratory symptoms improved at weekends or during vacation periods. However, lung function tests showed that there were no significant changes in FVC or FEV_1 over the course of a working day, and no individuals with occupational asthma could be identified. The possibility of a “healthy worker” effect was not investigated. The authors attributed the respiratory morbidity and pulmonary impairment among solderers to irritation of the airways by non-rosin components of solder fume.

The results of a recently completed, unpublished study of 7 soldering factories are also available (HSE, 1995). In total, groups of 235 exposed workers (82 male, 153 female) and 82 unexposed controls (40 male, 42 female) were compared after Institute of Occupational Medicine-based health questionnaires had been completed with the assistance of a trained interviewer. The exposed workers included solderers (20%), assemblers (60%), supervisors (6%) and quality control staff (14%). Job-related symptoms were classified as respiratory symptoms, cough and cough attacks, chest problems, nasal problems, eye problems or hand problems. After controlling for the effects of age and smoking status, there was no significant difference between the numbers of exposed and control workers reporting at least one respiratory symptom. Overall, there was a significantly higher proportion of exposed workers reporting at least one symptom, but this difference was only evident amongst female workers. Exposed females had a higher prevalence of respiratory symptoms than exposed males and controls, but this was not statistically significant. The prevalence of nasal problems was statistically significantly increased when exposed females were compared with unexposed females. The amount of time spent in a job with exposure to rosin fume appeared to have no effect on the number of reported symptoms. The possibility of any “healthy worker” effect was not studied.

The activity reported to cause the greatest prevalence of cough attacks, chest, nose and eye problems was manual soldering, but this was not investigated in detail. Worker exposure levels varied significantly across the factories but not the sexes. When workers were grouped according to exposure level, the prevalence of respiratory symptoms was greatest in workers with the highest exposure. However, the small numbers involved meant the significance of this finding

could not be established, and overall this small-scale cross-sectional study does not provide any evidence for markedly increased respiratory morbidity among solderers.

The fourth negative report concerns a cross-sectional study of female solderers in 2 electronics factories in Singapore (Lee *et al*., 1994). The solderers worked with rosin-cored solder flux in the absence of local exhaust ventilation; no exposure data were available. Liquid flux ("rosin type") was also used. The study excluded workers on permanent night-shift, part-time workers and technicians who were not hand solderers. Since the study group of 150 solderers included only 3 current and 3 ex-smokers, all 6 were also excluded from analysis. The control group of 52 age-matched female administration staff from the same factories were all non-smokers. A respiratory questionnaire was completed by interview with a trained investigator and the Chinese on study (101 solderers and 51 controls) undertook lung function tests at the start of a weekly shift. In addition, all the subjects were instructed on the correct use of a peak flow meter, and requested to make at least 4 peak expiratory flow rate (PEFR) measurements during each of 4 consecutive working days.

Solderers reported a significantly higher prevalence of work-related eye and nose irritation. There were relatively low, non-significant prevalences of cough (4.9%), breathlessness (2.8%) and wheeze (0.7%) among the solderers, and no respiratory morbidity in the controls. The lung function parameters were within the predicted ranges and no difference was observed between solderers and controls. Similarly, there was no difference in diurnal variation of PEFR in 134 solderers and 43 controls. The only significant finding was a slight decrease in the age-adjusted FEV_1/FVC ratio when the 36 solderers with 5 years or more potential exposure to soldering were compared with the 65 employed for less than 5 years. No cases of occupational asthma were observed, but the authors could not discount a "healthy worker" effect or asthma in night-shift workers. Overall, no definite conclusions can be reached from this small-scale study.

SUPPORTING EVIDENCE

There is no information available regarding specific antibodies in solderers with asthma associated with exposure to rosin-based solder fume.

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C26: SOME SOFTWOOD DUSTS

SUMMARY AND CONCLUSION

Occupational exposure to cedar dusts is associated with the development of a well documented asthma with an estimated prevalence of at least 13%. Immunoglobulin E (IgE) antibodies to plicatic acid, a component of western red cedar (WRC), have been found in patients with this asthma, correlating with their reaction in specific bronchial challenge tests. There is also some evidence that plicatic acid has a direct, histamine-releasing action. It seems that WRC asthma is not related to irritation of the airways, whereas other softwoods have occasionally been associated with the development of asthma that does appear to be irritant in nature.

There is sufficient evidence to conclude that some softwood dusts meet the revised EU criteria (1996) for classification as respiratory sensitisers (causes of asthma) and labelling with R42.

INTRODUCTION

Softwood dust is a general term covering a wide variety of wood dusts derived from mainly coniferous trees (gymnosperms). Woods have a complex composition, with main structural components such as cellulose and lignin, and a range of organic compounds known as “extractives”.

The following information has been summarised from an HSE Criteria Document for an Occupational Exposure Limit, where a more detailed critical appraisal of the available data can be found (Minty *et al*., 1996).

EVIDENCE FOR WORK-RELATED ASTHMA

Exposure to Western Red Cedar (WRC) dust produces in some workers an asthmatic syndrome characterised by wheezing, cough, nocturnal attacks of breathlessness, rhinitis and conjunctivitis. The majority of workers who develop asthma to WRC do so in the first five years of exposure, many in the first year. An organic component of these cedars, plicatic acid, has been implicated as the causative agent.

Although there are many published reports of occupational asthma associated with the use of WRC, only two have included bronchial challenge testing of patients in a blinded manner with either the wood dust or plicatic acid and control dusts or extracts. In both of these studies, patients with WRC-related asthma reacted positively at challenge to WRC dust and plicatic acid, but not to control preparations (Gandevia and Milne, 1970; Lin *et al*., 1995).

Further studies which have included normal or asthmatic controls indicate that the reactions seen at challenge are not related to non-specific irritation of the airways. There are also several studies producing positive, bronchial challenge results that included the use of control dusts or extracts, but were apparently performed in a non-blinded fashion. In a survey of 154 workers, 25% had either active, or a history of, asthma; positive challenge responses were obtained in 53% of the asthmatics and 9% of those with cough, but no others (Mue *et al*., 1975). This indicates a prevalence of at least 13% of work-related asthma specifically due to WRC. Another study investigated 332 patients with WRC-asthma (average latency 44 months), all of whom reacted to plicatic acid but not to saline at open challenge (Paggiaro and Chan-Yeung, 1987).

Other woods implicated include Eastern White Cedar, which also contains plicatic acid. Three cases have been reported of asthma associated with the use of California redwood (Chan-Yeung and Abboud, 1976; doPico, 1978). These subjects reacted positively to bronchial challenge with redwood dust, but not to control agents (pine sawdust, chalk, phenol/saline) or a WRC extract, indicating that the causative agent of redwood asthma is not the same as that of WRC asthma.

Asthmatic symptoms in response to exposure to other softwood dusts (spruces, firs, pines, cedar of Lebanon) has been rarely reported, and the available evidence indicates that they may be related to irritation of the airways.

SUPPORTING DATA

A proportion of workers with WRC asthma have specific IgE antibodies to plicatic acid - human serum albumin conjugate. For instance, in 2 studies 23% and 44% of WRC-asthmatics who gave a positive bronchial challenge had increased specific IgE antibodies to this conjugate (Tse *et al*., 1982; Paggiaro and Chan-Yeung, 1987). Neither control subjects nor WRC-asthmatics who failed to react at challenge had such antibodies.

Positive intradermal or skin prick tests with WRC extracts or plicatic acid occur with a greater frequency in symptomatic workers compared to exposed asymptomatic individuals, or to unexposed people, although some researchers have found little or no activity. Some other wood extracts (fir, maple, pine, redwood, spruce) have occasionally induced skin reactions.

In vitro experiments indicate that plicatic acid may have a direct histamine-releasing effect on cells (Frew *et al*., 1993).

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C27: SPIRAMYCIN

SUMMARY AND CONCLUSION

Spiramycin causes asthmatic symptoms in some exposed workers, and a number of bronchial challenge tests have been positive. The limited data indicate a prevalence of 6% of occupational asthma confirmed by bronchial challenge. No evidence indicating involvement of the immune system in induction of the asthma is available.

There is sufficient evidence to conclude that spiramycin meets the revised EU criteria (1996) for classification as a respiratory sensitiser (a cause of asthma) and labelling with R42.

INTRODUCTION

Spiramycin is a macrolide antibiotic manufactured as a fine white powder (Davies and Pepys, 1975). No published data on irritancy are available, although it was referred to as irritant in one occupational asthma study (Moscato *et al*., 1984).

EVIDENCE FOR WORK-RELATED ASTHMA

Reports of occupational asthma associated with the use of spiramycin are scarce and studies generally poorly conducted. Typical characteristics of occupational asthma, such as latency and experiencing relief away from work, have been noted (Davies and Pepys, 1975; Paggiaro *et al*., 1979). In a study of 51 workers exposed intermittently to spiramycin, the prevalence of asthmatic symptoms increased slightly from 12% (no exposure) to 19% (exposure); however, the proportion of workers with airways that were hyperresponsive to methacholine decreased with exposure (19% to 14%), as did those with occupational rhinoconjunctivitis (41% to 31%); moreover, one person who had no previous exposure to spiramycin suffered a significant increase in bronchial hyperresponsivess on first exposure (Malo and Cartier, 1988). None of these workers showed significant daily changes in their peak flow rates measured over a week of exposure.

A single case-report exists of a man with spiramycin-associated occupational asthma, who underwent single-blinded simulated occupational bronchial challenge with either lactose powder or varying concentrations of spiramycin in lactose (Davies and Pepys, 1975). He gave positive, late reactions to higher concentrations (0.08 - 0.8%) of spiramycin, but not to lactose or a lower spiramycin concentration (0.008%).

When 51 workers in a factory processing spiramycin were assessed, 14 had a history of occupational asthma and/or had hyperresponsive airways (Malo and Cartier, 1988). Of these, 12 underwent simulated occupational bronchial challenge with lactose or neat spiramycin powder; it is unclear if this testing was blinded or open. Three subjects gave positive reactions (all immediate, two being prolonged for several hours). The other nine workers, 4 of whom had hyperresponsive airways, failed to react to challenge, indicating that the reactions obtained in the other 3 were likely to have been specific to spiramycin. This study thus indicates a prevalence of 6% of occupational asthma confirmed by bronchial challenge.

A total of 4 other cases have undergone apparently open bronchial challenge with spiramycin. One man gave a late reaction to 50% spiramycin in lactose, but not to 0.04% or lactose alone, whereas poultry feed containing spiramycin induced only a borderline response (a decrease in forced expiratory volume in one second of 14%) in a woman occupationally exposed to this mixture (Paggiaro *et al*., 1979; Letourneux *et al*., 1987). She failed to react to feed that did not contain spiramycin. Finally, an aerosolised solution of spiramycin adipate induced bronchial reactions at challenge in two people who developed occupational asthma after using this compound (Moscato *et al*., 1984). One of these also reacted to spiramycin base and to adipic acid, suggesting that in this person, both components of the molecule were involved in the reaction.

SUPPORTING DATA

There are no specific immunoglobulin E (IgE) data. Total IgE levels were moderately raised in 2 people but normal in another 2 (Letourneux *et al*., 1987; Moscato *et al*., 1984; Paggiaro *et al*., 1979). Skin prick tests could not be interpreted in workers exposed to spiramycin or in non-

occupational asthmatic controls (Malo and Cartier 1988). The test was negative in one other case (Paggiaro *et al*., 1979). In a poorly-reported study of 305 workers involved in antibiotic production, 41 had positive skin tests, but since it was not stated what proportion were intradermal or patch tests, it is not possible to draw any conclusions (Nava, 1976).

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C28: TETRACHLOROPHTHALIC ANHYDRIDE

SUMMARY AND CONCLUSION

The available studies on tetrachlorophthalic anhydride (TCPA) include a number of positive bronchial challenge tests and indicate that it can induce occupational asthma. The immunological data suggest an allergic mechanism for induction of the asthma, although in one study antibody responses corresponded to exposure rather than to symptoms. Supporting evidence is provided by the close structural relationship to phthalic anhydride, for which there is a substantial body of information indicating a causal association with asthma.

There is sufficient evidence to conclude that tetrachlorophthalic anhydride meets the revised EU criteria (1996) for classification as a respiratory sensitiser (a cause of asthma) and labelling with R42.

INTRODUCTION

Tetrachlorophthalic anhydride is one of the acid anhydrides, which are irritant to eyes, skin and respiratory mucosa (Venables, 1989). It acts as a cross-linking agent in the production of epoxy resins used in the manufacture of plastics, paints and electronic components.

EVIDENCE FOR WORK-RELATED ASTHMA

In a factory where about 350 workers were exposed to an epoxy resin powder containing TCPA, 7 women developed respiratory symptoms within 2 years of TCPA being introduced into the factory (Howe *et al*., 1983). None of these woman had a history of respiratory or allergic disease. Airborne concentrations of TCPA were not available for this period but were probably high, since the resin powder could be seen throughout the factory (Venables *et al*., 1985). Symptoms included wheezy breathlessness, cough, chest tightness and conjunctivitis, and were clearly work-related. Four of the women underwent single-blinded bronchial challenge tests using a range of TCPA concentrations up to about 1mg/m^3, at least 4 months after they had last been exposed in the workplace. At this time their asthmatic symptoms had improved, and none showed bronchial hyperresponsiveness to histamine. Non-irritant challenge conditions in controls were not determined. All four subjects reacted positively at challenge with TCPA, giving 2 dual and 2 isolated late responses, and failed to react to control dusts. A good linear dose-response relationship was obtained, and it was calculated that a 15% fall in forced expiratory volume in one second (FEV_1) would be expected following exposure to 0.025% (0.99 mg/m^3) TCPA (Venables and Newman Taylor 1990).

A cross-sectional study was carried out at the same factory approximately a year after the 7 women had developed symptoms and subsequently left their jobs (Venables *et al*., 1985). During this time, measures had been taken to control exposure. A greater proportion of the factory workers (4-10%) reported work-related nasal symptoms than did the office workers (1.5%), but incidences of work-related chest symptoms were similar (1-4%). The nasal symptoms may have been due to irritation. There were no further cases of asthma which could be convincingly associated with exposure to TCPA.

In a workforce of 34 employees at a plastics factory, 5 developed shortness of breath, wheezing and cough which worsened over the working week and improved on days not at work (Schlueter *et al*., 1978). Dust levels were not measured, but were “thick enough to reduce vision to a few feet”. Various powdered chemicals were used, but the respiratory problems were reported to have developed after TCPA was introduced into the process, with a latent period of two months to two and a half years before symptoms developed. A further 10 of the 34 employees suffered mucous membrane irritation during heavy exposure. Three of the 5 subjects underwent apparently open bronchial challenge with TCPA dust, and all gave late responses with FEV_1

decreases of between 20 and 47%. However, the specificity of these reactions is uncertain due to the lack of appropriate controls.

In addition, TCPA has been implicated in other reports of work-related asthma, but where co-exposure to other agents thought to cause occupational asthma has occurred (Grammer *et al*., 1987; Liss *et al*., 1993). However, specific bronchial challenges were not performed in these studies, and no firm conclusions can be drawn for TCPA.

SUPPORTING DATA

Specific immunoglobulin E (IgE) antibody to TCPA-human serum albumin conjugate (TCPA-HSA) was significantly greater in 7 women with TCPA-associated asthma compared to both an exposed, non-asthmatic group and 7 non-exposed controls; levels for the latter 2 groups were similar (Howe *et al*., 1983). Specific IgG was not measured. All 7 asthmatic subjects, but none of the controls, gave immediate skin test reactions to TCPA. A follow-up study showed that specific IgE antibody levels dropped progressively with a half-life of a year, though the sera of those who had undergone bronchial challenge testing showed a temporary increase in specific IgE levels measured 2-3 months after the challenge (Venables *et al*., 1987).

A cross-sectional study was later carried out on 350 workers, including 54 office staff, at the same factory (Venables *et al*., 1985). The original 7 women who had developed asthma were not included. Twenty-four (8%) of the factory workers, but none of the office workers, had specific IgE higher than the normal range, and 11 of these had positive skin reactions to TCPA-HSA. A further 2 people had skin reactions but not increased specific IgE. The sera of 29% of the exposed workers contained specific IgG to TCPA.

In a smaller study, the presence or absence of IgE or IgG specific to TCPA-HSA, or positive skin prick tests, did not correlate with whether or not exposed workers had developed occupational asthma (Grammer *et al*., 1987). Other findings suggested that the levels of these specific antibodies tended to correspond with degree and length of exposure rather than being related to symptoms (Liss *et al*., 1993).

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C29: TRIMELLITIC ANHYDRIDE

SUMMARY AND CONCLUSION

A number of toxic syndromes which involve respiratory reactions have been identified in workers exposed to trimellitic anhydride dust or fume. The respiratory reactions include asthmatic symptoms, of either immediate or late onset, and rhinitis. In some individuals known to suffer from trimellitic anhydride-associated respiratory illness, exposure to very low airborne concentrations of the anhydride can provoke symptoms. There is strong evidence of an involvement of the immune system in the pathogenesis of these syndromes.

There is sufficient evidence to conclude that trimellitic anhydride meets the revised EU criteria (1996) for classification as a respiratory sensitiser (a cause of asthma) and labelling with R42.

INTRODUCTION

Trimellitic anhydride is a versatile chemical intermediate with principal uses in the production of plasticisers, wire enamels, surface coatings and wall and floor coverings.

The following information has been summarised from an HSE Criteria Document for an Occupational Exposure Limit, where a more detailed critical appraisal of the available data can be found (Ridgway *et al*., 1996).

EVIDENCE FOR WORK-RELATED ASTHMA

Trimellitic anhydride-related illness involving mainly respiratory symptoms, observed in a significant proportion of exposed workers at a US chemical plant, was first described by Zeiss *et al* in 1977. Three clinical syndromes believed to involve the immune system (together with a fourth, irritant condition) have since been described (Ahmad *et al*., 1979; Zeiss *et al*., 1992).

The first syndrome is characterised by asthma and rhinitis which begins after a latent period varying from 2 weeks to 4 years, but then comes on immediately after exposure. For some affected individuals exposure to very low concentrations of the anhydride can provoke symptoms. The second condition (late onset respiratory systemic syndrome or “trimellitic anhydride-flu”) involves a local respiratory reaction and systemic effects: coughing, wheezing and dyspnoea are generally observed 4 to 8 hours after a workshift, often accompanied by malaise, chills, fever, myalgia and arthralgia. Thirdly, there is a pulmonary disease/anaemia syndrome, a potentially fatal illness involving both respiratory and systemic effects, observed only in a small number of workers exposed to fume produced by spraying hot pipes with a resin containing trimellitic anhydride. The effects, observed after a latent period of several weeks, include dyspnoea, pulmonary infiltrates and anaemia.

SUPPORTING DATA

There is strong evidence that the immune system is involved in trimellitic anhydride-related illness (Zeiss *et al*., 1977; Patterson *et al*., 1979; Patterson *et al*., 1981). The asthma and rhinitis syndrome is associated with a positive skin prick test to trimellitic anhydride-human serum albumin (HSA) conjugate and with the presence of immunoglobulin E (IgE) antibodies specific to trimellitic anhydride-HSA. The late onset respiratory systemic syndrome is associated with the presence of elevated serum levels of specific IgG and IgA antibodies. However, skin prick tests with trimellitic anhydride-HSA are negative and the presence of specific IgE antibodies cannot be demonstrated.

Although there are no internationally-validated predictive methods for respiratory hypersensitivity, the potential of trimellitic anhydride to induce such a condition has been investigated in a number of animal studies (Botham *et al*., 1989; Leach *et al*., 1988). These showed that the animals can

become sensitised to trimellitic anhydride following intradermal induction in guinea pigs and inhalation induction in rats. In guinea pigs, the effects were associated with immunological changes and included bronchoconstriction, altered respiratory rate, and the presence of inflammatory exudate in the airways. The findings in rats provided strong evidence that the immune system has an important role in mediating the lung toxicity induced by trimellitic anhydride in that species.

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C30: COFFEE BEAN DUST

SUMMARY AND CONCLUSION

The results of several studies that have included specific bronchial challenge testing indicate that coffee bean dust has induced occupational asthma in a substantial number of exposed workers. Estimation of the true prevalence of this asthma is made difficult by the potential for coffee workers to be exposed to an allergen derived from castor bean. The presence of specific immunoglobulin E (IgE) has been demonstrated by skin prick and *in vitro* immunological tests, the findings showing an apparent association with respiratory symptoms.

There is sufficient evidence to conclude that that coffee bean dust meets the revised EU criteria (1996) for classification as a respiratory sensitiser (a cause of asthma) and labelling with R42.

INTRODUCTION

Workers from both the “developing” and the “developed” world are exposed to coffee bean dust during processing (Uragoda, 1988; O’Hollaren, 1992). In many cases, concomitant exposure to castor bean dust also occurs, apparently due to the contamination of the sacks in which the coffee beans are packed (Patussi *et al*., 1990). Castor bean dust is clearly a cause of occupational asthma (HSE, 1997). Immunological tests have shown that there is no significant cross-reactivity between green coffee bean and castor bean, indicating that different allergens are involved, and that the one derived from castor beans is the more potent (Thomas *et al*., 1991; Romano *et al*., 1995).

EVIDENCE FOR WORK-RELATED ASTHMA

A study was made of 22 coffee-roastery workers who all had work-related allergic symptoms such as sneezing, nasal itching, wheezing and cough (Osterman *et al*., 1985). All underwent specific bronchial and nasal challenge tests with an extract of green coffee bean; there was no mention of the use of a control challenge or whether the tests were carried out in an open or blinded manner. Eight workers reacted to bronchial challenge, 2 giving late reactions, and 7 to nasal challenge. All those reacting to the nasal test also reacted to bronchial challenge, and all had moderate-to-severe symptoms. Peak flow measurements taken over a working week were unhelpful.

Two asthmatic workers from a coffee-processing plant were challenged by inhalation of green coffee bean extract, apparently in an unblinded manner (Karr *et al*., 1978). Both workers gave significant falls in forced expiratory volume in one second (FEV_1) in comparison with baseline values obtained using control exposures of saline. A control subject who had asthma that was not related to coffee beans failed to react. There were no late reactions up to the end of the measurements at 12 hours.

Of 9 workers in the coffee-processing industry complaining of chest tightness and difficulty in breathing, 6 were found to have symptoms of occupational asthma and 8 of rhinitis (Zuskin *et al*., 1985). All 9 were given bronchial challenges with extracts of coffee. A control challenge using saline was carried out, but it was unclear if the tests were blinded, and the response was only followed for 20 minutes after challenge. Four of the subjects (all with asthma) reacted with significantly decreased FEV_1 to green coffee, while none of them reacted to roasted coffee.

The same researcher studied another population of 31 coffee workers and found only one case of asthma, although there were significant increases in the prevalence of respiratory symptoms such as chronic cough and dyspnoea compared to a group of matched controls (Zuskin *et al*., 1988). Four of the 9 coffee workers who underwent bronchial challenge tests responded, giving decreases in FEV_1 in the range 20–62%. Studies with healthy volunteers not occupationally exposed to coffee indicated that the dust or an extract could have an acute bronchoconstrictive

effect on the airways that was presumably not immunologically mediated (Zuskin *et al*., 1985, Zuskin *et al*., 1991).

There have also been reports of single cases in which workers who have developed occupational asthma after a latent period of 3 to 10 years have reacted to bronchial challenge with green coffee bean extract (Wallenstein and Schoneich, 1983; Musken *et al*., 1992; Lemiere *et al*., 1996). In one study, however, challenge tests proved negative (Sonneville *et al*., 1982).

Overall, these studies provide reasonable evidence that coffee bean dust can induce occupational asthma in exposed workers.

There have also been a few cross-sectional studies reporting respiratory symptoms in coffee factory workers. It may be difficult, however to estimate the prevalence of asthma induced by coffee bean dust itself, because of the possible presence of castor bean dust as a contaminant. One questionnaire assessment of 372 workers in 2 coffee-processing plants gave estimated prevalence's for occupational asthma of 0.5% and 4.0% (Jones *et al*., 1982). However, there was no control group for this study.

In a study of a coffee-manufacturing plant, 34 (16%) of the 211 workers reported asthma, with 30 (14%) claiming that symptoms persisted throughout the year (Romano *et al*., 1995). A further 22 (10%) reported oculorhinitis occurring in the absence of asthma. In this study, environmental dust from the factory was analysed and found to contain both green coffee bean and castor bean.

In another cross-sectional study, involving 21 workplaces, 959 workers were exposed to coffee dust, and in 2 workplaces there were 128 unexposed people (Sekimpi *et al*., 1996). The group of exposed workers had a higher prevalence of cough and phlegm, but only slightly more chest tightness and wheeze, than the control group. Rhinitis and conjunctivitis after starting employment were also increased, and there was a highly significant post-shift drop in FEV_1 in exposed workers compared to controls.

In a population of coffee workers in which allergy to castor bean was confirmed, 19/150 (13%) reported work-related respiratory symptoms; the prevalence in 47 unexposed controls was not quoted (Thomas *et al*., 1991).

Overall, these data indicate that a significant proportion of coffee workers suffer from occupational asthma, although it is not possible to distinguish the relative contributions of coffee bean and castor bean dusts to the induction of the condition.

SUPPORTING DATA

Skin prick tests have been carried out in a considerable number of studies, and reactions have consistently been found in a proportion of workers exposed to green coffee bean (Karr *et al*., 1978; Zuskin *et al*., 1981; Jones *et al*., 1982; Osterman *et al*., 1982; Wallenstein and Schoneich, 1983; Osterman *et al*., 1985; Zuskin *et al*., 1985; Zuskin *et al*., 1988; Patussi *et al*., 1990; Thomas *et al*., 1991; Glauser *et al*., 1992; Musken *et al*., 1992; Romano *et al*., 1995; Lemiere *et al*., 1996; Treudler *et al*., 1997). There was a good agreement that the proportion of exposed workers giving positive prick tests was approximately 9–15%. Several of these studies investigated the correlation between the presence of respiratory symptoms and skin prick reactivity, generally finding clear positive associations (Osterman *et al*., 1982; Osterman *et al*., 1985; Thomas *et al*., 1991). In two of these studies, there was also a general trend of increasing proportion of workers having positive skin prick test with increasing period of employment, up to 6–11 years. After this time the proportion decreased, possibly indicating a "survivor" effect with affected workers leaving after 6–8 years.

Most of the studies referred to above have also measured specific IgE using a radioallergosorbent test (RAST) method. The prevalence of positive RAST in an exposed population was 12%, similar to that found for skin prick tests (Jones *et al*., 1982). Positive RASTs

were found in all those workers with moderate-to-severe allergic symptoms, with negative tests being given by those without symptoms (Osterman *et al*., 1985). In contrast, in another study the association between work-related symptoms and a positive RAST result was not significant, although positive RAST results correlated with skin prick reactions (Thomas *et al*., 1991).

Finally, RAST inhibition test have shown that the same allergens are present in both green and roasted coffee, but in greater quantity in the green bean (Lemiere *et al*., 1996)

Overall, these studies show that some workers exposed to coffee bean develop specific IgE to the allergen, with indications that this is more likely to occur in those with respiratory symptoms than those without.

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C31: EGG PROTEIN

SUMMARY AND CONCLUSION

Studies amongst populations of workers indicate that workplace exposure to egg protein can lead to the induction of occupational asthma, which can result in a substantial proportion of the work force being affected. These findings are supported by adequately conducted bronchial challenge tests. Positive animal tests also provide support, as does the presence of asthma in humans who have become allergic to egg via the dietary route. An immunological response involving specific immunoglobulin E (IgE) has been demonstrated in many workers, but its relevance to clinical disease is uncertain.

There is sufficient evidence to conclude that egg protein meets the revised EU criteria (1996) for classification as a respiratory sensitiser (a cause of asthma) and labelling with R42.

INTRODUCTION

Eggs are a commonly used food to which workers are exposed occupationally during the processing of egg products or the use of eggs in, for instance, glazing baker products. Hypersensitivity to egg proteins is commonly encountered in people with food-induced allergies, for which the major allergens are ovalbumin and ovomucoid. Although dermatitis is the most common manifestation of dietary egg allergy, asthma and rhino-conjunctivitis occur as reactions to food ingestion. Asthma has been reported as occurring in 5 – 26% of all reactions to egg ingestion, as well as coming on due to inhalation of egg products during food production in the home (Dannaeus and Inganas, 1981; Langeland, 1983; Bernstein *et al*., 1993; Fremont *et al*., 1997).

EVIDENCE FOR WORK-RELATED ASTHMA

A man developed occupational asthma after working for six years with egg spray in the confectionary industry (Blanco-Carmona *et al*., 1992). He underwent apparently blinded bronchial challenge with a dilution of egg white or buffered saline, as did 2 asthmatic controls not previously exposed to egg by inhalation. He gave a positive early response to the egg white but not the buffer; the two controls failed react.

After eight months of working in the manufacture of egg white-derived lysozyme, a man developed asthma related to lysozyme exposure (Bernstein *et al*., 1993). A specific bronchial challenge test took place on separate days with a lactose control and lysozyme powder. He gave an early response to lysozyme but not lactose. He also had showed work-related decrease in peak flow over 18 days.

In a cross-sectional study in an egg-processing factory, 94 workers were assessed by questionnaire, and 23 reported at least one episode of wheezing, shortness of breath or chest tightness in the preceding month (Bernstein *et al*., 1987; Smith *et al*., 1987). The remaining 71 were asymptomatic. Thirty-one workers participated in a more detailed follow-up, of whom 13 were symptomatic and 18 without symptoms. Of the 25/31 who participated fully in the study, 5 were diagnosed as having occupational asthma by the physician involved, and had variable peak flow measurements. At least one reported a latent period (4 months) between the start of exposure and the development of symptoms. Re-examination of the screening questionnaires indicated that another fiver workers probably had occupational asthma, and of these 3 had left employment prior to follow-up. Thus the overall estimated prevalence from this study was at least 5% (5/94) and possibly as high as 11% (10/94).

In a follow-up study in two other egg-processing plants, 58 workers reported work-related asthmatic symptoms while 130 did not (Smith *et al*., 1990). Medical follow-up revealed that 37 had physician-diagnosed occupational asthma, though only 18 of these had a significantly

variable peak flow. Using the criteria of diagnosed occupational asthma plus two or more positive sin prick responses to egg allergens (see “supporting data”, below), the prevalence in various parts of the factories varied between 0 and 12% (5%-12% where present).

Four out of 13 bakery workers who were exposed to sprayed hen’s egg solution developed symptoms consistent with work –related asthma (Edwards *et al*., 1983). In another study, a bakery worker also developed occupational asthma after using a similar egg spray, but since he was also allergic to wheat and rye flour it is not possible to be certain that his asthma was induced by egg (Todaro *et al*., 1993).

SUPPORTING DATA

Many workers who have been exposed occupationally to egg have given positive skin prick tests to various components of egg including lysozyme, ovomucoid, ovalbumin, conalbumin, egg white and “egg” (Edwards *et al*., 1983; Edwards *et al*., 1985; Bernstein *et al*., 1987; Smith *et al*., 1990; Blanco-Carmona *et al*., 1992; Bernstein *et al*., 1993). In one of these studies, a positive skin prick test was significantly associated with the presence of work-related respiratory symptoms and a diagnosis of occupational asthma (Smith *et al*., 1990). Specific IgE as measured by radioallergosorbent test (RAST) has been found to the same egg fractions as above, and inhibition studies have indicated some cross-reactivity between lysozyme and ovomucoid (Edwards *et al*., 1983; Bernstein *et al*., 1987; Bernstein *et al*., 1993). In contrast to the skin prick test results, Edwards *et al* (1983) found that the presence of specific IgE as measured by RAST did not correlate with the presence of symptoms. The presence of specific immunoglobulin G (IgG) was not related to symptoms (Bernstein *et al*., 1987).

The presence of asthmatic symptoms as part of the clinical picture of food allergy to egg also provides supporting evidence that egg protein can induce asthma.

No internationally validated animal tests are currently available that allow prediction of the ability of a chemical to induce asthma in man. However, evidence that ovalbumin has the potential to cause respiratory sensitisation, with the presence of specific IgG, has been obtained in guinea pigs after induction by either the inhalation or intraperitoneal route (Karol *et al*., 1985; Karol *et al*., 1989). Challenge was by the inhalation route in both studies.

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C32: FISH PROTEINS

SUMMARY AND CONCLUSION

Exposure to aerosols generated during the cleaning of various species of fish has been shown to induce occupational asthma. Although only one study has included bronchial challenges, the quality of the remaining studies is sufficient to provide further good evidence. The prevalence when using automatic gutting machines was as high as 75% in one study.

There is sufficient evidence to conclude that fish protein meets the revised EU criteria (1996) for classification as a respiratory sensitiser (a cause of asthma) and labelling with R42.

INTRODUCTION

Manual gutting of fish has been carried out for centuries, but it has not been until the introduction of automatic machines that cases of occupational asthma have begun to be reported. These machines produce aerosols that certain fish protein and may also be contaminated with bacterial products (Sherson *et al*., 1989; Douglas *et al*., 1995).

EVIDENCE FOR WORK-RELATED ASTHMA

Within three months of the opening of a salmon processing plant with automated machines, 24 out of the 291 workers developed occupational asthma (Douglas *et al*., 1995). Diagnosis was made on the basis of a new history of asthma, work related symptoms and pulmonary function changes; there were no specific bronchial challenge tests. The latent period for the development of symptoms varied from 2 weeks to 3 months. The original 291 workers, who were exposed to respirable fish aerosol at up to 3.14 mg/m^3 were compared with a further 37 who joined after ventilation was improved to achieve levels of 0.09 mg/m3. None of these new workers developed occupational asthma. When the 291 workers were graded according to severity of symptoms, the groups showed a severity related increase in the percentage with specific immunoglobulin E (IgE) to salmon serum; 85% of the group with most severe symptoms had specific IgE compared to 3% in asymptomatic workers. Occurrence or specific immunoglobulin G (IgG) ranged from 28% in exposed workers without symptoms to 62% in the most severely affected group. Salmon serum antigen was identified in the aerosol produced by the machine.

In a case control study at the same factory, 13 affected cases without previous history of asthma were compared with 36 controls (Douglas *et al*., 1995). Following the improvement in ventilation, the pulmonary function of the cases improved. There was a significant association between the degree (but not the length) of exposure and specific IgE and IgG production.

All 8 production workers at a small trout-processing factory complained of rhinitis and/or asthma associated with working near an automatic gutting machine (Sherson *et al*., 1989). The latent period before the start of symptoms ranged from one week to eleven years. Pulmonary function studies, bronchial responsiveness to histamine and peak flow variation confirmed that 6 of the workers had occupational asthma (a prevalence of 75%), with a further one being a possibility. No specific bronchial challenge tests were carried out. The water from the gutting machine was found to be contaminated with bacterial growth and edoxtoxin, and air collected above the machine grew several species of bacteria. Specific IgE as measured by radioallergosorbent test (RAST) was definitely positive to scraped trout skin in only one person, and to contaminated water from the gutting machine in two people. None were definitely positive to salmon. It is not clear how much bacterial contamination played a part in the reactions obtained, but the latent period suggests involvement of an allergic reaction to a protein component in the contaminated water.

Two people who cleaned fish in fish factories developed occupational asthma with latent periods of a few weeks and one year (Rodriguez *et al*., 1997). It is unclear whether automatic gutting machines were in use. Neither subject had a previous history of allergies, although one man

(patient 2) developed a food allergy to fish after he had developed occupational asthma. Peak flow measurements were more variable at work than off work, but the differences were generally unconvincing. However, specific bronchial challenge tests, apparently carried out in an open manner, with extracts of a range of fish species were positive in both subjects (patient 1: hake, salmon, plaice, tuna; patient 2: salmon), whereas the control, house dust mite, proved negative. Negative findings were also obtained with the fish extracts in three asthmatic controls who were not allergic to fish. Patient 2 suffered a severe anaphylactic reaction after intradermal injection with trout extract, and so was not challenged by inhalation with this fish. Both patients had specific IgE to a range of fish extracts, which included plaice, salmon, trout, hake, tuna and anchovy, as measured by RAST and skin prick test.

SUPPORTING DATA

Allergic reactions after eating fish are well recognised, and in one group of patients, 54% suffered wheezing or chest tightness after ingesting fish (Helbling *et al*., 1996). Specific IgE testing revealed significant cross-reactivity between several species of fish. In another study, 21 out of 197 children with IgE-mediated fish hypersensitivity showed allergic reactions (wheezing and urticaria) after accidental inhalation of fish odours or fumes (Crespo *et al*., 1995). These studies provide evidence that asthma commonly occurs in people who are allergic to fish.

A chef who had developed occupational asthma to lobster also gave a strong skin prick test haddock and cod, suggesting a secondary allergy to these fish, or a cross-reactivity between crustacean and fish protein (Patel *et al*., 1992). This study does not provide strong evidence that haddock or cod can induce occupational asthma.

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C33: HENNA

SUMMARY AND CONCLUSION

The ability of henna to induce occupational asthma has been confirmed by bronchial challenge testing. The underlying mechanism appears to be immunological in nature, and measurements of specific immunoglobulin E (IgE) in exposed workers indicate that at least part of the allergenicity is due to a minor component or impurity that is present at higher concentration in black as compared to red henna.

There is sufficient evidence to conclude that henna meets the revised EU criteria (1996) for classification as respiratory sensitiser (a cause of asthma) and labelling with R42.

INTRODUCTION

Henna is a plant-derived dye that is used world wide to colour hair and skin. It can have different biologicalorigins and pigment from a number of sources may be called henna. Other plant materials are often added to add bulk to black, but not red, henna and these materials included ground castor bean, which is known to be able to induce asthma. One of the principal components of henna is 2-hydroxy-1, 4-naphthoquinone (Frosch and Hausen, 1986; Crane *et al*., 1997).

EVIDENCE FOR WORK-RELATED ASTHMA

There are a few reports of asthma associated with using henna in which the subjects have undergone bronchial challenge. Control powders were used in most cases, though challenges were apparently not blinded.

Sixty five workers participated in a study of four UK cosmetics factories in which henna was used, of whom 44 underwent spirometry and three took serial peak flow measurements (Crane *et al*., 1997). Fifty percent of the 44 showed an obstructive pattern (forced expiratory volume in one second (FEV_1) < 80% of predicted), but only one showed a fall in peak flow after working with henna. An earlier pilot study had indicated that about a quarter of the people working with henna suffered from breathlessness and/or wheeze, while 14% had asthma diagnosed by their doctors. However, it is not known to what other substances these workers were exposed. Seven subjects with respiratory symptoms and specific IgE in their sera (see following section) underwent bronchial challenge with black henna and flour dust on separate occasions. Five showed a significant fall in FEV_1 with henna, giving early reactions with one late reaction, but failed to react to flour. Exposure to the black henna made the airways of all seven of these subjects more hyperresponsive to histamine.

Starr and colleagues (1982) reported on 2 hairdressers with henna-related asthma; bronchial challenge with henna was clearly positive in one; both failed to react to flour dust. One female hairdresser with conjunctivitis, rhinitis and asthma gave no lung function changes on bronchial challenge, but did have a nasal response (Pepys *et al*., 1976). However, this subject also reacted to persulphates, and the induction of her asthma cannot be specifically ascribed to her exposure to henna.

SUPPORTING DATA

In case reports of henna-associated asthma, skin prick or scratch tests to henna dye have been positive (Pepys *et al*., 1976; Starr *et al*., 1982; Frosch and Hausen, 1986; Majoie and Bruynzeel, 1996; Scibilia *et al*., 1997). Where the types of dye have been specified, reactions have generally been positive to black henna but negative to red, and there are also negative findings with pure 2-hydroxy-1, 4-naphthoquinone. Thus the allergen seems to be either a minor component of henna or an impurity, found at highest concentrations in black henna.

The detection of specific IgE as measured by a radioallergosorbent test (RAST) is in agreement with the skin test results. In the largest study, 11 symptomatic workers had specific IgE to various types of henna (black, red, Egyptian, Sedra); when additional workers were studied, 15 had specific IgE to black henna, 10 to red henna and 20 to castor bean (Crane *et al*., 1997). The total number of participating workers was not stated. RAST inhibition studies showed cross-reactivity between castor been and black henna, and between red and black henna, but not between castor bean and red henna.

Overall, these studies indicate that both red and black henna are allergenic, but that black henna in addition contains other allergen(s), including castor bean. There are insufficient data to attempt to correlate the presence of specific IgE with exposure or presence of symptoms.

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C34: NICKEL SULPHATE

SUMMARY AND CONCLUSION

The findings of a number of studies, taken together, provide good evidence that nickel sulphate can induce asthma at work. Although only one of these studies concerns a series of subjects with asthma, the others comprising reports of single cases, they generally incorporate well-controlled bronchial challenge tests that confirm the causative role of nickel even in the presence of potentially confounding exposures. The process underlying the asthma seems to have an immunological component.

There is sufficient evidence to conclude that nickel sulphate meets the revised EU criteria (1996) for classification as a respiratory sensitiser (a cause of asthma) and labelling with R42.

INTRODUCTION

Exposure to nickel sulphate, often in the form of an aerosol, occurs in the electroplating industry (Cirla *et al*., 1985). Nickel is also occasionally added as a matrix, in addition to cobalt, to tungsten carbide in the production of hard metal (Shirakawa *et al*., 1990). Contact sensitisation to nickel is common, particularly in association with the wearing of jewellery, and nickel sulphate is included in standard batteries for patch testing of humans in relation to allergic contact dermatitis.

EVIDENCE FOR WORK-RELATED ASTHMA

Over a 5-year period, an occupational health unit investigated 11 workers in small metal plating factories, who were suffering respiratory problems (Cirla *et al*., 1985). Seven of the subject had clear clinical diagnoses of asthma, while the other 4 had symptoms of rhinitis and chest tightness, but did not experience distinct asthmatic attacks. Brinchial challenge tests were carried out in all 11 using nickel sulphate aerosols, proving positive in 6 of the 7 asthmatic subject but none of the other 4. There were 3 dual and 3 late responses. The challenge tests were carefully controlled in that workers exposed to aerosols of copper or chromium salts in their jobs, in addition to nickel, were also challenged with these salts. Subjects only exposed to nickel at work were given iron sulphate as the control challenge. In addition, 2 volunteers with asthma that was not related to metal-plating were tested with nickel sulphate. All of these control challenges were apparently negative. Overall, this well-conducted study provides good evidence that nickel salts can induce asthma.

A recent report describes an electroplating worker identified at a specialist lung clinic as suffering from occupational asthma induced by nickel (bright *et al*., 1997). The case is unusual in that the asthma started after an accidental high acute exposure, arising from the failure of extraction fans on the plating baths. Although the subject was exposed to both chromium and nickel in his job, the findings of single-blinded bronchial challenge tests indicated that nickel was the primary inducing agent: a late reaction was obtained with nickel chloride at 0.1mg/ml, while for potassium dichromate a concentration of 10mg/ml was needed to elicit bronchial reactions. A serial peak expiratory flow record was completed by the subject for a period of 41 days at and away from work, and it provided further clear evidence for occupational asthma.

A report of a well-conducted study describes a worker who developed asthma shortly after starting a new job electroplating with nickel and chromium (Novey *et al*., 1983). Bronchial challenge tests were conducted that simulated work-place exposure to fumes; double-blind testing was attempted in that the test solutions of nickel sulphate and chromium sulphate looked reasonably similar, and the subject was unable to distinguish between these solutions and 2 control solutions matching for colour and smell. Nickel sulphate produced a dual response, consisting of an immediate reaction with asthmatic symptoms and a larger late response at 3-4.5 hours that required medical intervention. With chromium sulphate challenge, there wee also immediate asthmatic symptoms but no late reaction up to 5 hours, when recording stopped.

There wee no reactions to either of the control solutions, and 2 asthmatic control subjects showed no effects. Overall, the findings indicate that exposure to nickel was involved in the induction of the asthma in this worker.

Another case report describes a metal polisher who developed asthma that was apparently related to the work environment, and whose job for 11 years had involved rubbing down the nickel surface of bumpers using an aluminium oxide grinding paper (Block and Yeung, 1982). Presumably unblinded bronchial challenge testing with work-place dust and with nickel sulphate produced immediate falls in forced expiratory volume in one second; there were no late reactions. Control tests with aluminium oxide and mahogany dust were negative, and a control asthmatic subject did not react to nickel sulphate challenge. Overall, this report provides further evidence that nickel can induce asthma.

There is a further case of a male subject who noticed dyspnoea, wheezing and cough a few months after starting electroplating with nickel and chromium (Malo *et al*., 1985). A bronchial challenge test with a relatively high concentration of nickel sulphate (10 mg/ml) caused a late asthmatic reaction that involved a 45% decrease in the forced expiratory volume in one second (FEV_1) and required medical treatment after 7 hours. A further, even more severe asthmatic attack occurred during the following night, and again this was resolved using a bronchodilator. A control challenge using saline gave a small immediate fall in FEV_1 but no late reaction. Although there is no indication that the challenge tests were blinded, and no control subjects or other solutions such as dichromate were tested, overall the pattern and magnitude of the responses obtained provide reasonable evidence that nickel was involved in the induction of asthma in this subject.

An earlier report from the same authors describes a man who developed cough, dyspnoea and wheezing after working with nickel sulphate in a metal-plating factory for 3 years (Malo *et al*., 1982). His symptoms occurred at work, and monitoring of his peak expiratory flow rates revealed variations suggestive of occupational asthma. Bronchial challenge tests (presumably unblinded) were negative for a saline control exposure, but showed an immediate response to inhalation of a 10 mg/ml solution of nickel sulphate. The maximum fall in FEV_1 was 34%, occurring 10 minutes after the end of the exposure, and there was no late reaction up to 8 hours. A control asthmatic subject with a similar degree of bronchial responsiveness to histamine, but who had never been exposed to nickel sulphate, did not react in a similar challenge test. Overall, these findings provide a further indication that nickel can induce asthma.

Another report concerns a female grinder of metal casings containing 9% nickel and 17% chromium (Estlander *et al*., 1993). She had suffered from allergic contact dermatitis related to nickel in jewellery since late childhood, but then started to get rhinitis and asthmatic attacks, as well as contact urticaria, at work. Bronchial challenge testing with nickel sulphate (10 mg/ml) led to a 22% fall in peak expiratory flow over 6 hours, while tests with much lower concentrations of potassium dichromate and with a lactose control were negative. In addition, 5 subjects with non-specific bronchial hyperresponsiveness did not react to the same concentration of the nickel solution. However, the challenge tests were apparently not conducted in a blinded manner, and overall the study provides only limited evidence that nickel was responsible for inducing the asthma in this patient.

An early case report describes a man who noticed cough, chest tightness and wheezing within 3 weeks of starting work at a nickel metal-plating company (McConnell *et al*., 1973). Symptoms occurred at work and were absent at weekends. Bronchial challenge testing with 10 mg/ml nickel sulphate led to a 35% decrease in FEV_1 compared with a baseline value, at 5 hours, when the test was ended to allow medical treatment. In comparison, a normal control subject gave a 12% fall in FEV_1 in a similar test. It does not appear that the challenge tests were conducted in a blinded fashion, the nature of the baseline testing is unclear, and overall these findings are of limited value to an assessment of the ability of nickel to induce asthma.

An investigation of cross respiratory reactivity between nickel and cobalt examined 8 male workers in a hard metal factory who had clear diagnoses of asthma and positive bronchial challenge tests to cobalt chloride, cobalt originally being thought to be the only causative agent (Shirakawa *et al*., 1990). Single-blinded challenge tests with nickel sulphate at concentrations up to 10 mg/ml proved positive in 7 cases, with 4 early, 3 late but no dual responses. In contrast, there were no reactions in similar tests with 6 asthmatic and 2 normal controls who had no known exposure to hard metal dust. Overall, these findings suggest that nickel as well as cobalt may play a part in the aetiology of hard metal asthma, but it remains unclear whether this is in the induction of the disease or merely in the elicitation of the symptoms.

A medical screening programme of 53 current workers at a nickel catalyst plant found none with work-related asthma (Davies, 1986). However, a limited review of past workers at the plant identified 3 cases of asthma apparently related to exposure to “nickel salts”. No bronchial challenge tests were conducted.

Finally, occupational asthma is also recognised among stainless steel welders, although a number of other metals, in particular chromium, are also present in these fumes, and investigations have not distinguished between them (Keskinen *et al*., 1980; Cirla *et al*., 1982).

SUPPORTING DATA

Immunological measurements have been made as part of many of the studies reporting asthma related to workplace exposure to nickel. Specific immunoglobulin E (IgE) has been detected (by radioallergosorbent test, RAST) in at least a proportion of test subjects in several studies (Malo *et al*., 1982; Novey *et al*., 1983; Cirla *et al*., 1985; Estlander *et al*., 1993). In another study, however, total IgE and specific IgE antibody levels were not significantly different from those of matched controls (Male *et al*., 1985). In an investigation of 8 patients with hard metal asthma originally presumed to have been inducted by cobalt, but showing cross respiratory reactivity to nickel, 4 had raised nickel-specific RAST scores, with the other 4 being similar to those in 8 control subjects (Shirakawa *et al*., 1990). This compared with 5 subjects who had positive RAST results for cobalt. The same group found that of 7 workers with hard metal asthma, 2 gave a positive lymphocyte transformation test with nickel (Kusaka *et al*., 1991). In the other 5, peripheral lymphocytes did not proliferate in response to nickel.

Skin prick tests conducted with nickel salts have generally been positive (McConnell *et al*., 1973; Block and Yeung, 1982; Malo *et al*., 1982; Estlander *et al*., 1993) – but negative for chromium and cobalt; Bright *et al*., 1997 – but negative for chromium), although there have also been some negative tests reported for nickel (Novey *et al*., 1983; Malo *et al*., 1985).

Finally, intradermal tests conducted using nickel sulphate in 8 patients with hard metal asthma were positive in 5 cases (Shirakawa *et al*., 1990). The same 5 subjects and one other also gave positive reactions to cobalt chloride.

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C35: OPIATES

SUMMARY AND CONCLUSION

There is a good body of evidence that opiates have the potential to induce occupational asthma, particularly given the likely circumstances of generally careful control of exposure in a limited number of production units. There is a plausible mechanism for asthma induction, one that is pharmacological in nature and related to the ability of opiates to cause bronchoconstriction. Such a mechanism explains why opiates can induce asthma in those who previously did not have it, and can also make pre-existing asthma worse.

There is sufficient evidence to conclude that opiates meet the revised EU criteria (1996) for classification as a respiratory sensitiser (a cause of asthma) and labelling with R42.

INTRODUCTION

Opiates or opioids are a group of drugs derived from opium, with morphine being medically the most important. Structurally closely-related opiates include heroin (diacetyl morphine) and codeine (methyl morphine), and these have similar pharmacological properties to morphine (Goodman and Gilman, 1990). Morphine is available as a range of salts including the sulphate (Merck, 1983). Opiate manufacture in developed countries is strictly controlled; there are apparently only three ethical manufacturing facilities in the United States (Biagini *et al*., 1990).

EVIDENCE FOR WORK-RELATED ASTHMA

There is only one study in which bronchial challenge testing has been carried out. A woman with no history of allergic disease who worked in a Polish pharmaceuticals plant, developed occupational asthma associated with working with morphine hydrochloride (Ulinski *et al*., 1996). Seventeen months after her last occupational exposure to morphine, when she was symptom-free, she was asked to work with morphine for 6 days, during which time her peak flow variability increased substantially and her symptoms returned. She then underwent a single-blind bronchial challenge with morphine hydrochloride, which induced a late asthmatic reaction involving a 39% decrease in forced expiratory volume in one second (FEV_1) and a 28% fall in vital capacity. There was no reaction to a control exposure to saline. She also underwent a nasal challenge, which also induced a significant late fall in FEV_1. An increased number of granulocytes (including eosinophils and basophils) was observed in nasal lavage fluid 3 hours after nasal or bronchial challenge, peaking at 24 hours; no such changes were seen with saline. Four control patients with bronchial asthma also underwent nasal challenge with morphine hydrochloride. None showed spirometric changes, and only a small increase in granulocytes was seen in nasal lavage fluid.

There are several other studies indicating that opiates can induce asthma in people who have not had it before, and that it can also make pre-existing asthma worse. There is a wide geographical distribution to these cases, which are described below.

One report describes a British pharmaceutical process worker who was previously free of asthma, but suffered from it when working with morphine dust (Agius, 1989). An earlier Russian study reported that asthma had been diagnosed in 16 workers who were involved in the production of morphine dust, with latent periods varying from several months to 7 years (Alenina *et al*., 1970). In another study, an association was found between the presence of apparently new symptoms and opiate exposure in a cross-sectional study of 112 workers (Agius, 1990). These symptoms comprised cough, wheeze or dyspnoea (4 workers), rhinitis (8) and sneeze (14), although apparently only 7 had current symptoms. In 43 employees, pre-existing respiratory symptoms were apparently made worse by their employment. Similar work-related symptoms were reported in a total of 5 people in Spain who worked with opium alkaloids, including morphine (Romaguera and Grimalt, 1983; Conde-Salazar *et al*., 1991).

In a group of 39 workers from a US factory that made morphine and related opiates, 8 complained of work-related asthmatic symptoms and 2 had suspect symptoms (Biagini *et al*., 1992). None of these workers had a history of pre-existing asthma, and 4 of them reported development of asthma within a year of beginning work. Investigation of lung function across a series of shifts, which can indicate work-related asthma, was inconclusive.

The asthmagenic properties of the raw material from which morphine is made have been investigated (Alday *et al*., 1991; Moneo *et al*., 1993). In a study of 28 workers in a pharmaceutical factory, 6 reported occupational asthma, but with maximal symptoms related to exposure to the raw material and no effects with the final products morphine and codeine. Although the symptomatic workers gave positive bronchial challenge tests (control subjects and symptom-free workers did not), and specific immunoglobulin E (IgE) was raised in all workers with symptoms, this only indicates that an unidentified component of the crude material was capable of causing asthma.

SUPPORTING DATA

Asthmatic reactions have also been reported in a non-occupational setting. One report describes the cases of three drug abusers in Britain who inhaled heroin regularly (Hughes and Calverly, 1988). One of the three addicts had pre-existing asthma, and another had had asthma in childhood. All three suffered severe asthmatic attacks and two died.

There is also a brief report of a man with no previous history of asthma who developed the disease after inhaling heroin daily for one month (Iglesias *et al*., 1994). When 100 asthmatics attending an American emergency department were compared with 100 non-asthmatics, there was a statistically significant association between inhaled substances of abuse (including opiates) and asthma exacerbation (Gaeta *et al*., 1996). No further details of these findings were provided. In a British study, 112 asthmatics were identified from a population of 2276 heroin addicts, the majority of whom took the drug by injection (Ghodse and Myles, 1986). Only 4 of the 112 had a history of allergy. In 31 (28%), there was a clear relationship between administration of the drug and the onset of asthma, which was reported to have occurred within hours or days of heroin use.

Overall, these studies indicate that inhalation or injection of opiates as substances of abuse can result in the development, or exacerbation, of asthma.

Opiates are powerful releasers of histamine, which can produce bronchoconstriction and local oedema in humans and animals, and this is the most likely mechanism by which they cause asthma. Central respiratory depression may also be important in depressing the normal compensatory responses to an asthmatic attach (Hughes and Calverly, 1988; Salonen, 1988).

When sera from 35 opiate workers were tested for the presence of morphine-specific antibodies, 20 were found to have IgG antibodies, but none had IgE (Biagini *et al*., 1990). Skin prick tests, which measure either IgE or histamine-releasing properties, were carried out in 33 of the original 39 workers, and compared with the results from 25 control subjects (Biagini *et al*., 1992). There was no significant difference in the proportion of people reacting to morphine between the groups (75 – 88%), these high values probably reflecting its histamine-releasing properties, although the opiate workers reacted to lower concentrations. Overall, these data do not provide any evidence that an allergic mechanism is involved.

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C36: STORAGE MITES

SUMMARY AND CONCLUSION

There is good evidence that exposure to storage mites, which commonly occur in stored foodstuffs such as hay and grain, can lead to the development of occupational asthma. The prevalence amongst farmers is 1–2%, with an indication that it may be higher (6%) amongst grain workers. There is good supporting immunological data indicating that an allergic mechanism is involved.

There is sufficient evidence to conclude that storage mites meet the revised EU criteria (1996) for classification as a respiratory sensitiser (a cause of asthma) and labelling with R42.

INTRODUCTION

Storage mites are found mainly in rural environments in stored food products such as grain and hay, with the highest contamination in conditions of high humidity. The species of storage mites most commonly found in the United Kingdom are Acarus Farris, A. siro, Tyrophagus longior and Lepidoglyphus (Glycyphagus) destructor (Cuthbert, 1990; Tee, 1994). It is unclear from the published literature which parts of the storage mite are involved in its allergenicity, although as with house dust mite it is likely to be the excreta, since this would form respirable particles.

EVIDENCE FOR WORK-RELATED ASTHMA

There have been a good number of bronchial challenges carried out with storage mite extracts. Although none has apparently been performed in a blinded manner, many have included suitable controls.

Twelve Swedish farmers with asthma, in whom specific immunoglobulin E (IgE) to storage mites had been detected, underwent bronchial challenge tests (van hage-Hamsten *et al*., 1988). In order to measure any non-specific irritative effects, two of the farmers were also challenged with Dermatophagoides pteronyssinus (house dust mite), and two individuals allergic to house dust mite were challenged with storage mite. All 12 farmers gave positive bronchial challenges to L.destructor (10 early and 2 dual responses), whereas the four control tests were negative. Farmers and controls did not react to the diluent.

Ingram and colleagues (1979) performed bronchial challenge tests with freeze-dried extracts of storage mite cultures mixed with lactose or with a control of yeast mixed with lactose. Three groups of Scottish farmers were tested, including 3 exposed but symptom-free people, 2 with work related rhinitis/conjunctivitis, and 4 with work-related asthma, and compared to three normal controls. Work-related symptoms were experienced when in barn or byre, especially when feeding cattle. Only in those with work-related asthma were positive bronchial challenge results obtained, and all 4 reacted to storage mite but not to the yeast control.

Kroidl (1994) studied 18 German farmers with asthma, which was thought to be due to storage mites in dusts. The subjects underwent bronchial challenge tests to extracts of storage mite and house dust mite, and all were reported to have specific IgE to both. All 18 farmers gave a positive bronchial challenge to storage mite but only 10 reacted to house dust mite, indicating a lack of cross-reactivity between the two mites. The reactivity to house dust mite may reflect the ubiquitous nature of this allergen.

Patients suspected of having allergic respiratory disease underwent bronchial challenge with storage mite extracts (Musken and Bergmann, 1992). The subjects did not come from any particular occupation, and no details of symptoms were provided, although all had given positive intradermal tests to storage mite. Of the 25 challenges performed, three were positive. The lack of

symptomatology and occupational data makes it difficult to determine the significance of the 22 negative challenges.

Occupational asthma related to *L. destructor* was investigated in 43 patients with a recognised IgE-mediated hypersensitivity to wheat flour (Armentia *et al*., 1992). Bronchial challenge tests, which were poorly described, were performed on 30 of the patients with asthma, and 13 reacted to an extract of the storage mite. In these cases it was not possible to tell whether the storage mite or the flour dust had induced the asthma.

Four single cases (3 European, 1 Canadian) of occupational asthma with positive bronchial challenges to storage mite extracts have also been reported (Warren *et al*., 1983; Korsgaard *et al*., 1985; Blainey *et al*., 1989; Del Mar Garces Sotillos *et al*., 1991). In the case reported by Warren, the subject reacted to one storage mite (L.destructor) but not to another (A. siro), indicating that these reactions can be specific.

A large number of nasal challenge tests have been performed with storage mite. While these do not provide the same strength of evidence as bronchial challenges, they do confirm the allergenicity of storage mites and their ability to provoke reactions in the upper respiratory tract.

In the study by Musken and Bergmann (1992), described above, 148 nasal challenges were carried out in people who had given positive intradermal tests with storage mite. Only about 10% were positive, but whether these findings correlated with symptoms was not discussed.

One hundred and six dairy farmers from Finland took part in a study of nasal challenges with storage mite species and cow dander extract (Terho *et al*., 1985). Eighty six suffered from rhinitis with or without asthma, while 20 were free of respiratory disease. Nasal challenge was carried out with storage mite in 63, with cow dander in 70 and with both in 27. Eighteen percent of the symptomatic farmers proved positive in nasal challenges to storage mite, and 20% to cow dander, with only a few reacting to both. None of those free from disease reacted to either. Thus in this study population, farmers tended to be allergic to either storage mite or cow dander.

A silo worker with rhinoconjunctivitis and respiratory ‘distress’ gave positive nasal challenge tests with L. destructor and T. putrescentiae, but was negative with house dust mite (Dickel *et al*., 1996).

There are no studies in which the prevalence of occupational asthma due to storage mite has been estimated from positive bronchial challenge tests. However, in two Scandinavian studies asthmatic symptoms have been correlated with the results of immunological tests, giving prevalences of 6.4% in a study population of 139 grain elevator workers and 2.3% in a subpopulation of 440 farmers (Revsbech and Andersen, 1987; van Hage-Hamsten *et al*., 1987). Using similar criteria, an Italian study of 149 farmers compared to 148 controls indicated a prevalence of approximately 1% (Patussi *et al*., 1994). Thus the prevalence in farmers is 1 to 2% with a higher rate (6%) amongst those working solely with grain.

SUPPORTING DATA

Several studies have demonstrated the presence of specific IgE to storage mite extracts by skin prick or radiolallergosorbent (RAST) tests, mainly in farmers or those exposed to grain dust (Ingram *et al*., 1979; Warren *et al*., 1983; Revsbech and Andersen, 1987; van Hage-Hamsten *et al*., 1987; Blainey *et al*., 1988; van Hage-Hamsten *et al*., 1988; Blainey *et al*., 1989; Iversen *et al*., 1990; Del Mar Garces Sotillos *et al*., 1991; Armentia *et al*., 1992; Musken and Bergmann, 1992; Marx *et al*., 1993; Kroidl *et al*., 1994). In some of these studies, positive specific IgE has correlated well with bronchial challenge results or with symptoms (Warren *et al*., 1983; Iversen *et al*., 1990). However, in other investigations there have been indications that the presence of specific IgE reflects exposure rather than the development of symptoms, and it was considered that only 10% of skin prick tests were clinically relevant (Musken and Bergmann, 1992; Marx *et al*.,1993).

Some cross-reactivity between D. pteronyssinus (house dust mite) and Aleuroglyphus ovatus (a storage mite) has been demonstrated by RAST inhibition (Silton *et al*., 1991). Two studies have also found general agreement between house dust mite and storage mite results in skin prick and standard RAST tests, although this could have been due to co-exposure or predisposition to developing allergy (atopy) rather than cross-reactivity (Ingram *et al*., 1979; Iversen *et al*., 1990). In contrast, other studies using skin prick and RAST tests have found little evidence for cross-reactivity between the two types of mite (Del Mar Garces Sotillos *et al*., 1991; Kroidl *et al*., 1994). The lack of cross-response to bronchial challenges with storage mite and house dust mite discussed above suggests that any cross-reactivity that exists may not be clinically relevant (van Hage-Hamsten *et al*.,1988).

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C37: ALPHA AMYLASES

SUMMARY AND CONCLUSION

There is a good body of evidence to indicate that fungal, bacterial and porcine pancreatic alpha amylases can cause occupational asthma which is mediated by an immunological mechanism involving immunoglobulin E (IgE). The main source of occupational exposure to fungal alpha amylase is in the baking industry. However, the precise incidence of occupational asthma in bakery workers specifically attributable to fungal alpha amylase, as opposed to flour or other allergens encountered in baking, is difficult to judge from the information available.

There is sufficient evidence to conclude that alpha amylases meet the revised EU criteria (1996) for classification as respiratory sensitisers (causes of asthma) and labelling with R42.

INTRODUCTION

Alpha amylases are enzymes which catalyse the hydrolysis of a-1®4 glucosidic linkages of polysaccharides such as starch, glycogen or their degradation products. Within industry the most commonly used alpha amylases are those of fungal and bacterial origin. These enzymes are not manufactured in the UK but are imported in the form of granulated or liquid preparations containing up to 25% enzyme. Fungal alpha amylase is used for the preparation of flour improvers and subsequently in flour milling and bread baking; also to a lesser extent in starch hydrolysis and alcohol production. Bacterial alpha amylase is used in the manufacture of detergents and animal feeds; also for starch hydrolysis, textile processing and brewing. It is not clear how many workers are exposed to concentrated fungal alpha amylase and bacterial alpha amylase preparations. However, many tens of thousands of workers are potentially exposed to lower concentrations of these enzymes. Small-scale laboratory uses have been identified for porcine pancreatic alpha amylase, but little information is available for this area of use.

The following information on fungal alpha amylase and bacterial alpha amylase has been summarised from HSE Risk Assessment Documents (HSE, to be published).

EVIDENCE FO R WORK-RELATED ASTHMA

Valdivieso *et al* (1984) carried out bronchial or nasal challenge tests on 4 bakers with symptoms of asthma (2) or rhinoconjunctivitis (2) relating to the use of flour or flour additives developing between 2 months and 18 years after starting work. In each case, symptoms improved at weekends and during holidays. The 2 subjects with symptoms of asthma underwent bronchial challenge testing using a double-blind protocol. One showed slight bronchial hyperesponsiveness with methacholine challenge, the other was unresponsive. Both had immediate asthmatic responses to fungal alpha amylase, showing a 22-25% drop in forced expiratory volume in one second (FEV_1) within 10-25 minutes of challenge. No late reactions were observed. Two asthmatic control subjects did not respond to fungal alpha amylase at a concentration 2 or 3 orders of magnitude greater than that administered to the bakers, indicating that the reactions in bakers were not due to direct airway irritation. The 2 bakers were also challenged with wheat flour; one showed some reduction in FEV_1, although the reaction barely met the criteria for a positive response. Nasal challenge tests were performed in the two bakers with rhinoconjunctivitis. It is not clear if these were also carried out blind. In comparison to the negative response obtained for a saline control challenge, fungal alpha amylase gave rise to marked immediate decreases in nasal inspiratory peak flow, plus nasal pruritus and measurable nasal secretions. A second nasal challenge with wheat flour extract was negative for both subjects. Two patients with hay fever did not respond when tested with fungal alpha amylase. Overall, this study provides good evidence that fungal alpha amylase can cause work-related asthma and allergic rhinitis.

Quirce *et al* (1992) studied 5 bakery workers with respiratory tract symptoms first occurring 1-33 years after starting bakery work. Bronchial challenge tests were carried out with fungal alpha amylase (all 5 subjects)and also with fungal cellulase (4), wheat flour (5), *Aspergillus sp*. (1) and *Alternaria tenuis* (1) on the basis of positive findings in skin prick tests and/or the detection of substance-specific IgE in sera. Each subject was challenged with progressively increasing concentrations, and all gave an immediate response to fungal alpha amylase (at least a 20% reduction in FEV_1) and one subject a late response (35% reduction in FEV_1 , 8-12 hours after exposure) at concentrations between 1:1,000 and 1:100,000 weight/volume. Each subject also responded to at least one other substance. A control group of 10 asthmatic subjects (not bakers) did not respond to challenge with fungal alpha amylase at a concentration of 1:10 weight/volume.

Moneo *et al* (1995), Alday *et al* (1995) Alvarez *et al* (1996) and Baur *et al* (1986) also obtained positive responses to fungal alpha amylase in bronchial challenge tests in asthmatic bakers. Moneo *et al* (1995) obtained positive responses from 8/25 bakery workers (7 of whom gave positive reactions in skin prick tests) compared with 0/10 non-exposed control subjects. The other 3 groups used positive skin prick test responses as a criterion for conducting a bronchial challenge, but did not conduct any challenges with control subjects. Alvarez *et al* (1996) obtained positive bronchial (4) or conjunctival (1) reactions from 5 bakers; positive reactions to wheat and soya bean flours were also obtained from some individuals in this group. Alday *et al* (1995) obtained positive reactions from 6/14 bakers and Baur *et al* (1986) from 4/4 bakers.

Bronchial challenge studies with fungal alpha amylase have also been carried out in pharmaceutical workers (Losada *et al.*, 1992) and enzyme manufacturing workers (Merget *et al.*, 1993). Six out of 14 workers challenged by Losada *et al* (1992) and 5 workers challenged by Merget *et al* (1993) had positive reactions. In addition, Losada *et al* (1992) obtained positive reactions from 6/11 workers given nasal challenges (by instillation of an fungal alpha amylase solution into one nostril and a saline control into the other nostril). Losada *et al* (1992) also challenged control subjects; 10 asthmatic non-exposed patients from the author's clinic and 10 asymptomatic workers with exposure to fungal alpha amylase were bronchially challenged and 10 non-exposed patients and 10 asymptomatic exposed workers were nasally challenged. No control subjects reacted.

Very few cases of occupational asthma due to bacterial alpha amylases have been reported. This may reflect different conditions of exposure in industries using bacterial alpha amylases compared with those using fungal alpha amylases.

Radermecker and Booz (1970) reported results of a blinded bronchial challenge test carried out on a worker exposed to a bacterial alpha amylase preparation in detergent manufacture. The worker developed symptoms of asthma after around 3 months exposure. Bronchial challenge tests were performed with an aerosol containing bacterial alpha amylase in a physiological solution and to the vehicle alone, with a 10-day interval between each challenge. The worker showed a dual response to bacterial alpha amylase, with a maximal fall in FEV_1 of 60%. The worker was also challenged under similar conditions with a subtilisin preparation to which he was exposed, producing a 70% drop in FEV_1.

Results reported in an abstract briefly note positive bronchial challenge results on single- blinded challenge in four UK detergent workers exposed to bacterial alpha amylase and presenting with symptoms of occupational asthma over the period 1994-1997 (Draper *et al.*, 1999).

One case of occupational asthma due to porcine pancreatic alpha amylase has been published (Aiken *et al.*, 1997). A laboratory technician had been using the enzyme for the preparation of tissue samples and developed symptoms of asthma after around 4 - 6 months. After a period of 4 weeks without exposure and medication, double-blind challenges were conducted in which the technician tipped lactose (control substance) or a mixture of lactose and porcine pancreatic alpha amylase between 2 trays for 5 minutes. Methacholine challenge revealed the technician to have hyperresponsive airways. The technician did not react to challenge with lactose but experienced

immediate and late reactions to porcine pancreatic alpha amylase, with a maximal reduction in FEV_1 of 75%. Rechallenge confirmed this positive reaction.

SUPPORTING DATA

Generally there was evidence of raised fungal alpha amylase- or bacterial alpha amylase-specific IgE (positive skin prick reactions and/or serological data) for all those who reacted to these enzymes on bronchial or nasal challenge, indicating an immunological basis to the asthma and rhinitis. The one worker with occupational asthma due to porcine pancreatic alpha amylase did not undergo any skin prick or serological testing. However, a separate study of pharmaceutical workers exposed to that enzyme found evidence of raised porcine pancreatic alpha amylase specific-IgE (Wiessmann and Baur, 1985), supporting an immunological basis for porcine pancreatic alpha amylase-induced occupational asthma.

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C38: BROMELAINS

SUMMARY AND CONCLUSION

Exposure to bromelains during bronchial challenge testing has produced positive results in 5 individuals considered to have developed occupational asthma due to their work activities. Ingestion of pineapple has also been shown to result in similar asthmatic responses to those produced upon inhalation exposure to bromelain. Detection of specific immunoglobulin E (IgE) to bromelain and positive skin prick tests suggest that the underlying mechanism of the asthma is immunological. Cross-reactivity between bromelain and papain (a structurally similar protease) has also been demonstrated.

There is sufficient evidence to conclude that bromelains meet the revised EU criteria (1996) for classification as a respiratory sensitiser (a cause of asthma) and labelling with R42.

INTRODUCTION

Bromelains are a group of closely related proteolytic enzymes present within the fruit, stem and leaves of the pineapple. They are glycoproteins with molecular weights of approximately 33 kdaltons, and near the enzyme active site the sequence of amino acids is similar to that of papain.

Bromelains are used as an aid to digestion and anti-inflammatory agent in pharmaceutical products, as a marker in some laboratory methods, and as a meat emollient (Galleguillos and Rodriguez, 1978; Baur and Fruhmann, 1979; Gailhofer *et al*., 1988; Valero *et al*., 1994).

EVIDENCE FOR WORK-RELATED ASTHMA

Two men employed at a pharmaceutical laboratory, one in the preparation of medicines (including one containing bromelain) and the second as a messenger within the same facility, reported symptoms suggestive of occupational asthma (Galleguillos and Rodriguez, 1978). The first subject experienced bronchial obstruction and rhinitis whilst working and was shown by spirometry to have completely reversible airways obstruction. No further asthma attacks occurred after he left his job. The second subject had suffered episodes of bronchial obstruction over a four-year period and also had rhinitis. Interestingly, in this subject the eating of pineapple resulted in similar asthmatic attacks.

Both subjects underwent single-blind bronchial challenges with bromelain in lactose, or pure lactose as a control, whereby they were required to pour each powder repeatedly from one tray to another. Initial baseline forced expiratory volume in one second (FEV_1) measurements were made and then at regular intervals for an hour. Measurements were also performed the next day to detect any late reactions. For the first subject an immediate 62% reduction in FEV_1 was obtained and there was also evidence of a late reaction, a 28% decrease in FEV_1. An immediate, 40% reduction in FEV_1 accompanied by rhinitis was produced in the second subject.

Bronchial challenge with a solution of bromelain, delivered by a nebulizer, produced an immediate asthmatic response in a female worker from a pharmaceutical factory, as determined by airway resistance measurements (Baur and Fruhmann, 1979). This individual had handled bromelain and papain at irregular intervals over a period of 10 years during which time she had experienced respiratory symptoms including wheezing and nasal discharge. During the bronchial challenge the subject's specific airway conductance fell by over 50%, indicating a positive test, then gradually returned to its initial value over a 5-hour period. This same individual also underwent oral challenge by eating a pineapple; shortness of breath occurred within 40 minutes of consumption, and there was a significant (33%) decrease in specific airway conductance between the first and third hour after. Similar bronchial challenges to bromelain as that described above were also conducted on 2 out of 6 subjects who were referred to by the study authors as

being “sensitized to papain”. Immediate asthmatic responses were produced in both cases, thereby demonstrating the potential for cross-reactivity between the closely related proteases, bromelain and papain.

An investigation of clinical symptoms was performed on 2 workers suspected of having developed occupational asthma whilst employed at a factory utilising bromelain in the preparation of film-coated tablets to aid digestion (Mattei *et al*., 1979). The first subject received exposure during the weighing and distribution of raw materials at the factory, whilst the second worker was responsible for packing the finished tablets. Both individuals were subjected to a bronchial challenge with bromelain, but no further details of how this was conducted were presented in the report. Both subjects experienced what was described by the authors as a “clear asthmatic attack”, but again no further information was provided.

Four workers employed in a diagnostic blood-grouping laboratory underwent investigation, having been suspected of developing occupational asthma as a consequence of exposure to powdered bromelain (Gailhofer *et al*., 1988). Repeated asthmatic-type symptoms including wheeze and rhinitis were reported, with 2 of the 4 workers also showing anaphylactic reactions following consumption of fresh pineapple. Similarly, severe asthmatic attacks ensued in 2 of the 3 subjects tested about 3 hours after skin pricks with bromelain.

In response to complaints of “respiratory problems”, an occupational health survey was conducted at a pharmaceutical factory using bromelain in the manufacture of anti-inflammatory drugs (Cortona *et al*., 1980). Of the 76 workers included in the survey, 7 were suspected of having developed occupational asthma; 4 had in the previous 15 months experienced moderate attacks at work and at night, whilst the 3 remaining individuals had a history over several years of asthmatic attacks arising at work and during the night, with 2 of them requiring treatment.

Symptoms of sneezing, rhinorrhoea and irritation and nasal congestion were reported in a female subject following nasal challenge with a fine intranasal spray of bromelain enzyme extract (Valero *et al*., 1994). Although this subject had not previously been directly exposed to bromelain in the work environment, she had apparently undergone ‘indirect’ exposure via contact with workers handling this enzyme in powdered form, and from the air conditioning venting from an adjacent room (where it was being handled) to where she worked in a pharmaceutical factory. Following careful control of her ‘environmental’ exposure to bromelain, this individual became asymptomatic.

SUPPORTING DATA

Specific IgE to bromelain was demonstrated using a radioallergosorbent test (RAST) in the female worker employed at the pharmaceutical factory investigated by Baur and Fruhmann (1979). A positive skin prick test was also given by this individual. Similarly, positive skin prick tests to bromelain were obtained in 5 of the 6 “papain-sensitive” group of individuals. This latter finding provides further evidence for the cross-reactivity between bromelain and papain.

Various tests including what appears to have been skin prick and passive transfer (Prausnitz-Kustner) tests were found to be positive for the 2 workers suspected of having developed occupational asthma described by Mattei *et al*., (1979), and for another 2 workers also employed at the same tablet-manufacturing factory. The work of these latter 2 individuals involved weighing and distribution of raw materials and the preparation of the film-coated tablets respectively. Bronchial challenge tests were not performed with these 2 workers since what was described as “bronchospastic symptoms” had arisen when the skin tests were done.

Bromelain-specific IgE was detected by RAST in all 4 subjects described by Gailhofer *et al* (1988), but a negative response to papain-specific IgE was produced. Skin prick tests to bromelain conducted on 3 of the 4 individuals were positive, with the resultant reactions persisting for a number of hours. In addition a comparative study was performed in which 17 other workers employed at the same diagnostic laboratory, who had at some point been exposed to bromelain,

were compared with a non-exposed group of 15 randomly-selected, healthy, sex-matched individuals within the same age range. Bromelain-specific IgE was detected in 7/17 exposed subjects compared to none of the controls. “Symptoms” reported to be due to “bromelain allergy” occurred in 4/17 exposed subjects compared to none of the controls. All 4 of these individuals demonstrated bromelain-specific IgE. Skin prick tests using bromelain and papain were conducted on 3/7 of the bromelain-specific IgE-positive subjects, and systemic anaphylactic reactions were observed which required intensive emergency treatment.

All 7 of the asthmatic subjects described by Cortona *et al* (1980) produced positive intradermal tests to bromelain.

Following the detection of positive IgE-mediated responses to bromelain and/or papain and a-amylase during routine monitoring, a full investigation of this was conducted at a pharmaceutical factory (Zentner *et al*., 1997). Amongst a population of 20 workers, 5 reported symptoms such as cough, dyspnoea and sneezing. Seven of the 20 workers produced a positive skin prick test to bromelain, with 5 of these also demonstrating specific IgE, as revealed by RAST. A control group of 10 unexposed workers produced a negative response to these tests.

Positive skin prick test results to bromelain were produced in 4/70 workers employed at the pharmaceutical factory studied by Galleguillos and Rodriguez (1978), with negative results being obtained for 100 control asthmatic subjects also tested.

A positive skin prick test was obtained for the female subject described by Valero *et al* (1994). Ten unexposed individuals were also included as controls and negative results were obtained.

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C39: CEPHALOSPORINS

SUMMARY AND CONCLUSION

Occupational asthma caused by exposure to cephalosporins has been demonstrated in a total of 8 workers who underwent bronchial challenge tests with different types of these semisynthetic antibiotics or the active nucleus component, 7-aminocephalosporanic acid. The available skin prick test results suggest an underlying immunological mechanism for the production of the asthma.

There is sufficient evidence to conclude that cephalosporins meet the revised EU criteria (1996) for classification as respiratory sensitisers (causes of asthma) and labelling with R42.

INTRODUCTION

Cephalosporins are semisynthetic antibiotics derived from the natural antibiotic cephalosporin C, which is produced by the mould Cephalosporium acremonium (Martindale, 1996). There is a close relationship between 7-aminocephalosporanic acid (the active nucleus) and 6-aminopenicillanic acid (the nucleus in penicillin) with both acids having in common a beta-lactam ring. The cephalosporins act via inhibition of bacterial cell wall synthesis.

EVIDENCE FOR WORK-RELATED ASTHMA

In a well-conducted study, a female subject was suspected of having developed occupational asthma as a result of exposure to a cephalosporin antibiotic (ceftazidime) during its manufacture and packaging (Stenton *et al*., 1995). A double-blind specific bronchial challenge was performed using either ceftazidime in phenol-saline or a saline control solution. A positive dual asthmatic response was induced at the highest concentration tested, whilst the lowest concentration, like the control, failed to induce a response. Rhinitis was also reported to occur, and a nonspecific bronchial challenge test using methacholine indicated moderate to very hyperresponsive airways.

Enjalbert *et al* (1980) undertook investigations of 4 suspected cases of occupational asthma arising from exposure to the cephalosporin cephradine. The 4 subjects involved were all employed in a factory manufacturing pharmaceuticals and had experienced “asthma-type” symptoms either whilst at work or during the night at home. Two of the subjects developed rhinitis during exposure to cephradine at work, whilst another reported upper respiratory tract irritation during exposure. All 4 of the cases displayed hyperresponsive airways when given acetylcholine in a nonspecific bronchial challenge test. A single-blind bronchial challenge was conducted whereby all 4 cases poured cephradine powder (10% in lactose) from one container to another for 10 minute periods up to a total of 40 minutes. Determinations of forced expiratory volume in one second (FEV_1) were conducted pre-exposure and at 10 minute intervals during exposure. Positive responses (18-60% reductions in FEV_1) were obtained for all 4 subjects. Of these positive responses, 3 were early occurring 10-25 minutes from the start of exposure, with the fourth being seen as a late response at 6 hours.

Two suspected cases of occupational asthma arising from exposure to cephalosporin products were investigated by Coutts *et al* (1981). In the first case, the male subject weighed out 7-amino-cephalosporanic acid (an intermediate in the manufacture of cephalosporins) and its tosylate dihydrate derivative, as part of a presumably single-blinded bronchial challenge test. Immediate (within 5 minutes of exposure) falls in FEV_1 of 27 and 20% were measured for 7-amino cephalosporanic acid and its tosylate dihydrate derivative challenge respectively. A control challenge using magnesium stearate produced no response. A similar investigation was performed on the second case, who was required for the bronchial challenge test to transfer 2 cephalexin derivatives (diluted in lactose) between trays for 30 minutes. In the first test using cephalexin dissolvate, an immediate 16% reduction in FEV_1 was measured, which increased in

magnitude to 30% in a repeat test. Challenge with cephalexin monohydrate produced a similar (30%) reduction in FEV_1, with no response being seen with the lactose control.

A very limited and briefly described case report of a male subject employed in the manufacture of cephalosporins for approximately 1 year, and exposed to cefmetazole and the cephalosporin chemical intermediate 7-aminocephalosporanic acid, is available (Fracchia *et al*., 1996). Nonspecific bronchial challenge with methacholine as well as specific challenges to what were described by the study authors as "samples of dusts of the antibiotics used by the patient" at work were undertaken. Apparently "a very high level of bronchial hyperreactivity to methacholine, and specific bronchial hyperreactivity to cefmetazole and 7-aminocephalosporanic acid" were detected.

Amongst a workforce exposed to 7-aminocephalosporanic acid during the manufacture of cephalosporins, 7 out of a total of 91 employees complained of asthma (Briatico-Vangosa *et al*, 1981). These 7 individuals experienced attacks of dyspnoea whilst at work but not outside; in 3 cases, treatment with steroids became necessary. All but one of the 7 had to be transferred from the cephalosporin synthesis department. A range of lung function tests conducted on the individuals when symptoms were quiescent gave normal results.

SUPPORTING DATA

Coutts *et al* (1981) obtained positive skin prick test results with 7-aminocephalosporanic acid and its tosylate derivative, and cephalexin dissolvate for the first and second cases respectively described above.

Skin patch tests using 7-aminocephalosporanic acid performed on the 7 suspected asthmatics investigated by Briatico-Vangosa *et al* (1981), produced positive results (immediate type response within 20 minutes of application) in 3 of the subjects. Five of these 7 subjects also underwent intradermal tests and a positive response was obtained in 3 of the cases.

Negative skin patch and intradermal tests were produced upon follow-up of the case report described by Fracchia *et al* (1996). However, the specific agent tested was not stated. A total immunoglobulin E determination proved normal.

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C40: COCKROACH MATERIAL

SUMMARY AND CONCLUSION

Although there is only limited evidence that exposure to cockroaches can lead to the development of occupational asthma, a good number of studies have linked the occurrence of asthma with environmental exposure to cockroach material, using evidence from specific bronchial challenge tests as well as the results of skin tests and radioallergosorbent test (RAST) measurements of cockroach-specific immunoglobulin E (IgE).

There is sufficient evidence to conclude that cockroaches meet the revised EU criteria (1996) for classification as a respiratory sensitiser (a cause of asthma) and labelling with R42.

INTRODUCTION

There are 7 or 8 indoor species of cockroach, with different ones predominating in different parts of the world. Dead cockroaches and/or excreta may remain in a building for long periods, and as they gradually disintegrate they become part of general house dust, with the highest concentration being found in the kitchen (Kang, 1976; Sarpong and Corey, 1998).

There are a number of potential antigens in cockroach-derived material, including those from the faeces, cast skins, whole bodies, eggs and saliva (Potera, 1997).

EVIDENCE FOR WORK-RELATED ASTHMA

There is only a little evidence for the induction of asthma by cockroaches occurring in the occupational setting.

A case report briefly describes a female animal attendant who handled cockroaches when cleaning their cages, and was also exposed to their saliva released as a defensive measure (Kanerva *et al*., 1995). She developed work-related asthma and rhinitis, as well as contact urticaria, which resolved when her exposure to the cockroaches ceased.

The experience of two entomologists and a laboratory worker is discussed very briefly by Bernton *et al*., 1972. After working with cockroaches for 8 years, one of the entomologists developed hay fever-like symptoms and asthma, as well as dermatitis, on handling them. The other entomologist was apparently obliged to wear a gasmask when dissecting cockroaches, to avoid ‘terrible fits of asthma’. The laboratory worker was reported to have suffered asthma attacks when in the presence of a particular species of cockroach, with direct contact not being necessary. Other species of cockroach did not cause similar asthma attacks

Finally, a brief report describes 3 research assistants involved with breeding cockroaches who developed rhinitis, one also showing symptoms of asthma (Zschunke, 1978).

SUPPORTING DATA

A good number of studies have linked the occurrence of asthma with environmental exposure to cockroach material, using evidence from specific bronchial challenge tests as well as the results of skin tests and RAST measurements of cockroach-specific IgE.

In a well-conducted study, 22 hospital patients with active, moderately severe asthma were given bronchial challenge tests with cockroach antigen (Kang, 1976). Sixteen of the subjects had proven positive in skin tests with cockroach antigen, while the other 6 were negative. For the bronchial challenges, paired tests (saline control and antigen) were carried out on consecutive days in a random sequence. Immediate bronchoconstrictive responses were noted following the antigen inhalation in 14 of the 16 skin reaction-positive asthmatics, with 13 of the 14 also showing

late reactions. The average decrease in forced expiratory volume in one second (FEV_1) in the 14 responders was 49%, while saline challenge in this same group had no effect. None of the 6 skin reaction-negative asthmatics showed a significant decrease in pulmonary function following antigen challenge. Finally, when 3 of the 16 skin reaction-positive subjects were challenged with grass or ragweed antigen, to which they did not react in skin tests, none gave a detectable bronchoconstrictive response. Similar findings were obtained in further work with 46 asthmatic patients in a study with a similar design (Kang *et al*., 1979), and together they provide good evidence that cockroach material may play a role in inducing asthma in the general population.

In another study with a similar design, 25 asthmatic patients with positive skin tests to whole body cockroach extract were investigated (Pola *et al*., 1988). Twenty-three of these subjects were found to have cockroach-specific IgE, and all of them reacted positively to bronchial challenge with the cockroach extract, 17 presenting only immediate asthmatic responses (averaging a 30% reduction in FEV_1), 5 a dual response (immediate and late, 30% and 50% reductions respectively) and 1 only a late response (45% reduction). The 2 patients who did not have cockroach-specific IgE, together with 10 control subjects, gave negative responses. Pretreatment with disodium cromoglycate prior to bronchial challenge in 5 of the patients resulted in total inhibition of both immediate and late responses.

Of 592 urban American asthmatic patients who had presented with recurrent symptoms including wheezing and shortness of breath, and objective signs of obstructive small airway disease, 283 had positive skin tests to extract of various cockroach species (Kang *et al*., 1992). In bronchial challenge tests, 101/116 of these 283 subjects gave asthmatic responses with the antigen, indicated by a reduction in FEV_1 of at least 15%. Of the asthmatics with negative responses to cockroach extract in skin tests, 10/11 gave negative responses to bronchial challenge while the other one showed a borderline decrease in FEV_1 of 16%.

Other investigations, but not using bronchial challenge testing, have linked the occurrence of asthma in groups of patients with the presence of sensitivity to cockroaches as indicated by positive skin reactions and/or specific IgE. One study involved measurement of skin test reactivity and specific IgE (assayed by RAST) to cockroach whole body and fecal extracts, in a group of patients with rhinitis and asthma living in an urban area in Spain (Ibañez *et al*., 1996). Of 171 consecutive patients, 44 had at least one positive skin test to one of the cockroach extracts, and 24 had at least one positive RAST. Similarly, a study which investigated a series of aeroallergens affecting 200 Malaysian urban asthmatic patients found that 87 of them showed skin prick test reactivity to cockroach allergen (Choon-Kook *et al*., 1998). In a study of 476 children, aged 4-9, with asthma in American inner-city areas, 37% were found by skin testing to be allergic to cockroach allergen, compared with 35% for dust-mite allergen and 23% to cat dander (Rosenstreich *et al*., 1997). Finally, a study of 196 asthmatic children, less than 3 years of age, living in a rural setting in America revealed that, out of a series of indoor allergens tested, the most common positive agent was cockroach allergen, with 51 children reacting to skin prick tests (Wilson *et al*., 1999).

Of 6 laboratory workers who were regularly occupationally exposed to cockroaches, 3 reported work-related nasal and ocular symptoms associated with xenografting and bleeding procedures (Steinberg *et al*., 1987). No symptoms of wheezing, chest tightness, cough, or shortness of breath were apparent. Skin prick testing and RAST were performed using various cockroach extracts, and 3 symptomatic workers and one asymptomatic worker gave a positive skin reaction to one or more of them. Negative skin prick tests were observed in 8 laboratory workers whose jobs did not involve exposure to cockroaches. Similarly, one symptomatic and one asymptomatic worker exhibited significant RAST binding above the mean of the 8 controls. A nasal challenge test using cockroach whole body extract was conducted on one symptomatic worker, and this resulted in a 69% fall in nasal airflow from baseline. No significant change was found using the same concentration of extract on nasal challenge of two individuals who had not shown a cutaneous reaction to cockroach.

In the case of occupational asthma described by Kanerva *et al* (1995), a positive skin prick test was obtained with cockroach saliva, and specific IgE to whole body extract and saliva was found by RAST. There is also a recent case report linking the development of asthma with domestic exposure to cockroach material by way of a positive skin prick test to cockroach extract (O'Connor and Gold, 1999).

No internationally-validated animal tests are currently available that allow prediction of the ability of a chemical to induce asthma in man. However, there is evidence that guinea pigs exposed to aerosolised cockroach allergen can develop an antigen-specific "asthma-like" airway obstruction (Kang *et al*., 1995; Kang *et al*., 1996; Zhou *et al*., 1997). A murine model of cockroach allergen-induced airway hyperresponsiveness and eosinophilia has also been reported (Campbell *et al*., 1998)

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C41: FLOUR DUST

SUMMARY AND CONCLUSION

There is an extensive body of evidence, both from epidemiological studies and case reports, that exposure to ‘flour dust’, as defined, causes occupational asthma in the baking industry. Flour dust contains a number of potential allergens including cereal antigens and enzymes. A number of reports have demonstrated positive skin prick tests and the presence of specific immunoglobulin E (IgE) to both these classes of antigen, suggesting an immunological mechanism. The results of these tests show an apparent association with allergic symptoms in exposed individuals.

There is sufficient evidence to conclude that ‘flour dust’ meets the revised EU criteria (1996) for classification as a respiratory sensitiser (a cause of asthma) and labelling with R42.

INTRODUCTION

Flour dust has been defined by the HSE, for the purpose of setting an occupational exposure limit, as “ the finely ground particles of cereals or pulses (including contaminants) which result from any grinding process and from any subsequent handling and use of that 'flour'. Any additives (eg flour improvers) are included in this definition only after they have been added to the final product mix.”

Thus defined, flour dust contains a number of potential allergens, the most important of which are cereal antigens and enzymes, particularly a-amylase. Published reports suggest that the relative potency of amylase as a sensitiser is greater than that of the cereal antigens, and it has been subject to its own review reported elsewhere in this Compendium.

In the UK flour is predominantly produced, by the milling industry, from wheat grain with subsequent use primarily as a baking ingredient to make a whole range of products including bread, rolls, cakes, pastries and pies. It is estimated that the flour mills employ around 5,000 people and that there are 95,000 employees in the UK baking industry with about 24,000 of these in occupations where there is a potential for exposure to flour dust.

The following information has been summarised from an HSE Risk Assessment Document, where a more detailed critical appraisal of the available data can be found (HSE, 1999).

EVIDENCE FOR WORK-RELATED ASTHMA

Flour dust is a well-recognised cause of occupational respiratory disease in humans. The consequences for the respiratory tract of occupational exposure to flour dust appear to have either allergic or non-allergic (irritant) elements (or both). The prevalence of work related respiratory symptoms has been variously reported to occur in 5 to 40% of all bakery workers.

In the UK, exposure to flour and grain dusts account for up to 8% of all cases of occupational asthma reported under the SWORD (Surveillance of Work-related and Occupational Respiratory Disease) project (Meredith *et al*., 1991; Meredith and McDonald, 1994; Ross *et al*., 1995). It is also a significant cause of disablement for which industrial injuries benefit is payable, accounting for 12% of new cases of asthma. It has been estimated that occupational asthma due to flour and grain dust has an annual incidence rate in the order of 286 to 409 per million bakery workers, within the 4 highest of any occupational grouping in the UK (Meredith *et al*., 1991; Meredith and McDonald, 1994).

Dual asthmatic reactions following bronchial challengen testing with the inhalation of flour (wheat or rye flour) was first reported by Hendrick *et al* (1976), although the nature of the late reaction in the two cases presented was unclear, being more characteristic of an allergic alveolitis.

Baldo *et al* (1980) describe one case of asthma in a baker who reported attacks of breathlessness following inhalation of both rye flour and wheat flour. On bronchial challenge testing there was an immediate asthmatic reaction to both flours which was more severe for the rye flour. Both cereal flours also provoked delayed asthmatic reactions, again more severe for the rye flour. No reactions were observed to a lactose control.

In a detailed investigation of 7 bakers with occupationally-related respiratory symptoms, Block *et al* (1983) performed bronchial challenge with rye and wheat extracts for the determination of antigen-specific bronchial reactivity. An immediate asthmatic response to antigen challenge was observed in 4 subjects, and all of these had a high level of cereal specific IgE antibodies, as measured by radioallergosorbent test (RAST). These 4 subjects had a history over several years of wheezing and chest tightness, whilst of those with negative challenge and non elevated IgE one had recurrent wheezing and cough associated with respiratory infections and 2 had productive cough only. Non-baker asthmatic controls had negative bronchial reactions to challenge with wheat or rye extract.

SUPPORTING DATA

In a cross-sectional study of dust exposure, respiratory symptoms, lung function (including bronchial reactivity) and sensitisation to flour in a British bakery, Musk *et al* (1989) studied 279 bakery workers, 35% of whom had positive skin prick tests to one or more bakery antigens (including mites, moulds, cereal antigens and enzymes).

Herxheimer (1973) reported that the prevalence of positive skin tests to wheat increased from 9% (of 880) in bakers recruits to 19% (of 290) by the end of the third working year to over 30% (of 37) by the fifth year, although this last figure may be high, being influenced by the relatively small numbers.

Thiel and Ulmer (1980) showed that 91% of bakers with respiratory symptoms related to exposure to flour had positive skin test responses to wheat and rye, whereas less than 5% of non-exposed control subjects had positive skin reactions to these materials. A strong positive association between wheat flour allergen exposure and wheat flour sensitisation (immunoassay for specific IgE antibodies) has also been reported (Houba *et al*, 1998).

The relative importance of the 4 flour fractions, albumin, globulin, gliadin and glutenin, in initiating type one hypersensitivity reactions has been investigated using RAST methods and immunoblotting. It was found that IgE antibodies from bakers with respiratory allergy bind to the water soluble fractions to a greater extent than to the less soluble gliadin and glutenin fractions (Baldo and Wrigley, 1978; Walsh *et al*, 1985; Walsh *et al*, 1987).

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C42: ISPAGHULA

SUMMARY AND CONCLUSION

Positive results have been reported in two specific bronchial challenge studies for a total of 5 subjects. Positive skin prick responses to ispaghula and the presence of ispaghula specific IgE are suggestive of an immunological mechanism for the asthma.

There is sufficient evidence to conclude that ispaghula meets the revised EU criteria (1996) for classification as a respiratory sensitiser (a cause of asthma) and labelling with R42.

INTRODUCTION

Ispaghula and psyllium are bulk laxatives obtained from various Plantago species. Ispaghula consists of the dried ripe seeds of Plantago ovata, while psyllium is derived from P. psyllium or P. indica (Martindale, 1996).

EVIDENCE FOR WORK-RELATED ASTHMA

A group of 6 nurses with a history of rhinoconjuncitivitis and/or asthma, thought to result from occupational exposure to ispaghula, were tested in a double-blind bronchial challenge study (Machado and Stålenheim, 1984). It was unclear from the report whether control subjects were also challenged. All of the nurses experienced pronounced rhinitis 15 minutes after challenge and 3/6 also reported moderate to pronounced cough/wheeze. In these 3 subjects falls in forced expiratory volume in one second (FEV_1) of 10, 30 and 53% were obtained, indicating 2 positive challenge results. No responses were reported following the control exposures.

In an earlier study, it was reported that a group of 6 nurses and 9 pharmaceutical workers who handled ispaghula products experienced a range of symptoms including rhinitis, itchy eyes, throat and hands, with dyspnoea and wheezy respiration reported in 4 of them (Machado *et al*., 1983). These 15 subjects took part in a specific bronchial challenge test to a commercial isphaghula preparation and a lactose control. It was not stated if the study was conducted blind and no control subjects were included. Following exposure to ispaghula, the most common symptom reported was rhinoconjuctivitis. In 5 subjects falls in FEV_1 of 12, 12, 20, 46 and 50% were recorded, indicating 3 positive challenge results.

SUPPORTING DATA

In a study of 92 workers involved in ispaghula production, 48 reported respiratory, eye, nasal or skin symptoms in a standard questionnaire on respiratory symptoms (McConnochie 0 *ET AL*., 1990). In skin prick tests, 39 of the 92 gave positive responses to a range of common allergens, with 5 responding to ispaghula. Serum IgE levels were elevated in 16 of the workers, and specific radioallergosorbent assay (RAST) determinations indicated that 9 were producing ispaghula-specific IgE.

In a short communication it was reported that of 90 nurses examined for ispaghula specific IgE in a RAST assay, bronchial challenge, and a skin prick test, 13 gave positive responses (Machado *et al*., 1982). In the same study it was also reported that of 60 workers examined from the pharmaceutical industry, 12 gave a positive response to the same set of tests.

The nurses involved in the study by Machado and Stålenheim (1984) were also given ispaghula orally one month after their bronchial challenge exposures. All 6 reported itching and rhinitis, with 2 also complaining of coughing and wheezing.

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C43: PSYLLIUM

SUMMARY AND CONCLUSION

Evidence is available from 3 surveys of occupationally exposed subjects indicating that psyllium can cause occupational asthma. These observations are consistent with clear positive results obtained in five specific bronchial challenge studies following psyllium exposure. The mechanism appeared to be immunological, as indicated by the presence of psyllium specific IgE and positive skin prick tests to psyllium.

There is sufficient evidence to conclude that psyllium meets the revised 0EU criteria (1996) for classification as a respiratory sensitiser (a cause of asthma) and labelling with R42.

INTRODUCTION

Psyllium and ispaghula are bulk laxatives obtained from various Plantago species. Psyllium is derived from Plantago psyllium or P. indica, while ispaghula consists of the dried ripe seeds of P. ovata (Martindale, 1996).

EVIDENCE FOR WORK-RELATED ASTHMA

Five nurses who had previously complained of rhinoconjuctivitis following occupational exposure to psyllium preparations took part in an apparently open specific bronchial challenge test (Cartier *et al*., 1987). No control subjects were included in this test. The response to a control substance, lactose, was also examined on a separate occasion. Falls in forced expiratory volume in one second (FEV_1) in the range 26-58% were observed in 4 of the subjects following exposure to psyllium. In the other nurse the immediate response to psyllium was so severe that pharmacological and mechanical interventions were required. Bronchial hyperresponsiveness, determined by nonspecific challenge testing with methacholine, was reported in 4 of the subjects.

When a group of 135 employees from a pharmaceutical company involved in psyllium production were examined for evidence of occupational asthma, nonspecific challenge testing with methacholine revealed at least mild bronchial hyperresponsiveness in 42 of them (Bardy *et al*., 1987). A total of 108 subjects were available for further examinations, with 18 being selected for an apparently open bronchial challenge test using psyllium. Five of these 18 showed a decrease in FEV_1 of greater than 20%, with a range up to 40%. A control substance (lactose) administered on a separate day gave negative results.

A study was conducted in connection with the evaluation of the effectiveness of a novel dust generating system for specific bronchial challenge tests (Cloutier *et al*., 1992). In this study 10 subjects, referred for investigation of occupational asthma, were exposed to psyllium dust via a mask over the face. A separate control exposure to lactose was included in the protocol, but it was not clear whether the study was conducted in a blinded fashion. A 20-35% fall in FEV_1 was observed in 6 of the subjects over a period of 2-30 minutes.

In a study of 162 healthcare workers with occupational exposure to psyllium-containing preparations, 20 reported respiratory symptoms such as wheezing, chest tightness or breathing difficulties, and 61 rhinoconjunctivitis (Malo *et al*., 1992). Specific bronchial challenge tests were conducted on 10 of these workers. A separate control exposure to lactose was included, but it was not indicated whether the study was conducted with blinding. Following the specific challenge, falls in FEV_1 were observed in 8 of the subjects, in the range 18-58%. A methacholine challenge test revealed nonspecific bronchial hyperresponsiveness in 9 of the 10 subjects given specific tests.

A case report describes the results of tests conducted on a subject who reported respiratory symptoms following dispensing of psyllium preparations (Schwartz *et al*., 1989). In comparison to

pre-exposure values, nasal airway resistance was increased up to 5-fold, specific airway resistance was increased by 16-25% and FEV_1 was decreased by 3 - 5%.

A briefly reported survey found that of 743 healthcare workers, 136 indicated that they had experienced rhinitis, runny nose, wheeze, shortness of breath or hives within 30 minutes of exposure to psyllium (Nelson, 1987). Such symptoms were also reported in 2 other surveys of occupationally exposed subjects (Bardy *et al*., 1987; Malo J-L *et al*., 1992).

Finally, anecdotal evidence is available from a good number of case reports indicating that psyllium exposure can cause symptoms of asthma, such as shortness of breath, coughing and wheezing (Freeman, 1974; Rosenberg *et al*., 1982; Gauss *et al*., 1985; Ponzer *et al*.,1986;0 SCOTT, 1987; Sussman and Dorian, 1990; Ford *et al*., 1992; Vaswani *et al*., 1996).

SUPPORTING DATA

A study of 135 workers employed at a pharmaceutical facility producing psyllium- based products found that 19% gave a positive response to psyllium in a skin prick test, and 25% had a positive radioallergosorbent test (RAST) for psyllium (Bardy *et al*., 1987).

In a study of 162 healthcare workers, clinical investigations found that 6 gave a positive skin prick test to psyllium and 20 a positive psyllium RAST (Malo J-L *et al*., 1992).

A number of case reports indicate that psyllium-specific IgE, as determined by RAST, was greatly elevated in subjects occupationally exposed to psyllium (Freeman, 1974; Rosenberg *et al*., 1982; Gauss *et al*.,1985; Ponzer *et al*.,1986; Scott, 1987; Schwartz *et al*., 1989; Sussman and Dorian,1990; Ford *et al*., 1992; Vaswani *et al*., 1996). Positive skin prick responses to psyllium were also reported in some of these case reports (Rosenberg *et al*., 1982; Ponzer *et al*., 1986; Sussman and Dorian, 1990; Ford *et al*.,1992; Vaswani *et al*., 1996). Overall, these data suggest an immunologically- mediated response to psyllium.

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C44: SOYBEAN DUST

SUMMARY AND CONCLUSION

Positive bronchial challenge results to soybean dust and/or its derivatives have been reported in 12 subjects suspected of developing asthma as a result of occupational exposure. In other investigations of workers, respiratory symptoms indicative of occupational asthma together with statistically significant decreases in lung function parameters have been demonstrated following exposure to soybean dust. In addition, there is a large body of evidence demonstrating a positive association between environmental exposure to soybean and the onset of asthmatic attacks in various parts of Spain in the 1980s. The common finding of specific immunoglobulin E (IgE) and positive skin prick tests to soybean and/or its derivatives is suggestive of an immunological basis for the mechanism of induction of the asthma.

There is sufficient evidence to conclude that soybean dust meets the revised EU criteria (1996) for classification as a respiratory sensitiser (a cause of asthma) and labelling with R42.

INTRODUCTION

Soybean (also known as soyabean) derives from the leguminous plant Glycine max and is a very rich source of protein. Its uses can be approximately divided into 3 groups; the whole bean, the oil and the meal (Wightman, 1938). Following cooking the whole beans can be eaten as a vegetable or used in soybean infant milk formulas and tofu. Following its extraction the oil has many uses including in the manufacture of margarine, cheese and mayonnaise. It is also widely used industrially, such as in the manufacture of paints, adhesives and fertilizers. Soybean lecithin is employed as an aid to hydration, fermentation, elasticity and preservation of bread. The meal is included in breakfast cereals and infant foods, and when ground into flour it is used either as pure soybean flour or mixed with other flours for use in the baking and cake industry.

EVIDENCE FOR WORK-RELATED ASTHMA

A recent study investigated two confectioners, a baker and a baker/confectioner who developed symptoms of cough, chest tightness, shortness of breath and wheeze (Quirce *et al*., 2000). Besides cereal flour, all 4 subjects routinely handled flour additives containing soybean flour and fungal amylase, and all had nonspecific bronchial hyperresponsiveness, as indicated by methacholine challenge tests. Following an initial control challenge with saline, specific bronchial challenge tests were carried out with increasing concentrations of water-soluble soybean flour extract, until decreases in forced expiratory volume in one second (FEV_1) of at least 20% were obtained. Three immediate and one dual (immediate followed by late) asthmatic responses were obtained.

Two bakers suspected of having developed occupational asthma to soybean lecithin in flour underwent specific bronchial challenge tests, with the saline used to dilute the lecithin being used as a negative control (Levaud *et al*., 1994). It is unclear whether the challenges were conducted in a blinded manner. Control subjects were also included at challenge and comprised 3 nonatopic volunteers and 3 asthmatic patients. Positive, early responses comprising 45 and 50% reductions in FEV_1 were seen with the 2 bakers, while the 6 control subjects gave negative responses following challenge.

A nonspecific bronchial challenge test using methacholine was performed upon a female worker employed in a food processing plant who had been exposed to soybean flour (used as a protein extender) on alternate days of employment (Bush *et al*., 1988). This worker had developed symptoms of wheezing, dyspnoea, rhinorrhoea and coughing which appeared within 15 minutes of being exposed to the flour, and usually disappeared 2 hours post-exposure, and the test confirmed hyperresponsive airways. A control challenge was also conducted whereby the worker was required to pour lactose powder from one beaker to another, and specific airways resistance

measured before and after pouring. No significant change in this parameter was observed following this control challenge. Finally, an identical inhalation challenge was performed to soybean flour, and an immediate, large increase in specific airways resistance was obtained. This was accompanied by the development of symptoms of sneezing, coughing, wheezing and shortness of breath necessitating medical treatment.

A small selection (2 bakers, one miller and 2 farmers) was made from a group of cereal workers diagnosed in a hospital department in Spain as having occupational asthma, in order to try to ascertain the underlying causative agent (Alvarez *et al*., 1996). Nonspecific challenge tests using methacholine indicated that 4 of them (the 2 bakers, the miller and 1 of the farmers) had hyperresponsive airways. The 5 subjects were then given specific bronchial challenge tests using aerosolized particles of soyabean, and again all but one of the farmers gave positive responses.

In a limited and briefly described case report, a positive challenge response was obtained in a female nurse's aid suspected of having occupational asthma who underwent a simulated workplace exposure involving the preparation of a "Soyaloid" (soybean powder and polyvinyl pyrrolidone) bath (Peters, 1965). The subject had complained about having recurring asthmatic attacks during the preparation of these baths such that medical treatment was considered necessary. The positive challenge response was accompanied by symptoms of allergic rhinitis and conjuntivitis. When the subject transferred to different work her symptoms ceased. Interestingly, hives and asthma-like symptoms were also seen to occur after the patient had consumed soybean pancakes.

An early case report of limited value is available that describes a male shipping clerk who apparently developed asthma in association with the arrival of soybean meal for storage in the room adjacent to where he worked at a factory where rosin was manufactured (Wightman, 1938). His asthma was reported to be worse whilst at work. He remained free from symptoms of asthma during a stay in hospital for non-asthma related medical treatment, but then within 1 day of returning to work developed asthma to the extent that medical treatment was required. Following a job transfer outside the plant he remained free of asthma for 5 months.

Another limited, early case report, describes a man who experienced attacks of asthma whilst employed as a bricklayer's "helper" in the reconstruction of an explosion-damaged soybean plant (Olsen, 1936). These attacks occurred after 6 months of beginning the reconstruction work and included symptoms such as dyspnoea and allergic rhinitis. The worker remained free from such attacks whilst away from the plant.

Zuskin *et al* (1988) carried out an investigation of respiratory symptoms and lung function in a group of 27 male workers exposed to soybean dust during its processing into animal feed. A control group of 21 workers employed as packers of nonalcoholic beverages in the plant were matched by sex and age. Most of the exposed and control group workers were smokers. Respiratory symptoms were assessed by means of a questionnaire and the determination of a number of lung function parameter values. Measurements were taken both before and after workshifts on Monday, the first day of the working week. Although there were no statistically significant differences in chronic respiratory symptoms between the exposed and control group, 2 of the soybean workers but no controls displayed symptoms described by the study authors as "characteristic of occupational asthma". Also, a statistically significantly higher prevalence of acute symptoms, including cough, dyspnoea, throat and eye irritation, were reported in exposed compared to control workers. Lung function parameter measurements in the soybean workers were statistically significantly reduced across the Monday workshift, and when expressed as percentages of the pre-shift values amounted to decreases of, for example, 2.7% for FEV_1 and 3.6% for forced vital capacity. It was also noted that in the exposed group there was a statistically significant reduction in measured pre-shift lung function parameter values compared to expected values. Similar findings to those reported in this study were also obtained in a follow-up investigation conducted on 19 of the 29 total workers employed at the plant (Zuskin *et al*., 1991).

SUPPORTING DATA

In the 1980s in Barcelona, Spain a number of epidemic outbreaks of asthma occurred resulting in emergency hospital admissions and in some cases death (Ortega *et al*., 1998; Becklake *et al*., 1999). The first noticeable outbreak arose in 1981 and between that date and 1986, a total of 12 such outbreaks were identified (Anto *et al*., 1996). Further investigation demonstrated that most of the asthma attacks occurred in areas within close proximity to the harbour.

Several well-designed investigations, including what Becklake *et al* (1999) described as "time-ecological" studies linking the outbreaks of asthma with soybean unloading at the harbour and a case-control study, were conducted. These provided what was considered by the Collaborative Asthma Group (a specially convened group set up in 1984) to be conclusive evidence for a causal relationship for the onset of asthma with exposure to soybean.

For the "time-ecological" studies the association between unloading of 26 products at the harbour and the occurrence of asthma outbreaks during 1985-1986 was assessed. It was revealed that during this period, all 13 asthma epidemic days coincided with the unloading of soybean. However, in contrast, in the remaining 486 days (when soybean was not unloaded), no asthma epidemics arose.

As part of the case-control study, specific IgE to soybean was measured by radioallergosorbent test (RAST) in the sera obtained from 74% of the asthma cases who suffered an attack during an epidemic episode, compared to only 4% of those asthma cases presenting on non-epidemic days (Becklake *et al*., 1999).

There is also a study of a group of 7 men and 8 women who attended 3 main hospitals in the port of Tarragona, Spain in November 1994 following an outbreak of asthma attacks (Ortega *et al*., 1998). All the subjects were interviewed within 1-3 months of the reported outbreak and a number of analyses conducted, including skin prick testing and determination of specific IgE to soybean seed. A positive skin prick test to soybean seed extract derived from that being unloaded at the port at the time of the attacks was obtained in 13 of the subjects, and specific soybean IgE was detected in the sera of 11 of them.

Gonzalez *et al* (1991) analysed serum samples collected from 32 patients who had attended the emergency department of a hospital in Cartagena, Spain during 2 asthma outbreaks which occurred in October 1987 and April 1988. Specific IgE to the shell proteins derived from a soybean sample taken from a cargo unloaded at Cartagena in October 1987 was demonstrated in 90% of the test sera. Specific IgE to soybean shell depleted grains was also detected in 13% of the test subjects. In contrast, no detectable levels of specific IgE to soybean components were identified in the sera taken from 32 control asthmatic subjects who received medical treatment at the same hospital on non-epidemic days. Positive skin prick tests to soybean extract were obtained with 87% of the test sera samples, whilst negative responses were found for the control sera.

In another similar type of study, Rodrigo *et al* (1990) investigated the sera from 4 different groups of 10 subjects; Group A comprised subjects who attended an emergency room of a major hospital in Barcelona, Spain due to the occurrence of an asthma attack on epidemic days, Group B consisted of individuals who attended the emergency room for an asthmatic attack on non-epidemic days, Group C were asthmatic subjects from other cities, and Group D were non-asthmatic individuals from Barcelona and were age and sex matched with Group A. Specific IgE to extracts of various soybean samples (prepared from soybeans unloaded on 2 epidemic days in 1987) was identified in the sera of all Group A subjects, whereas only 1 individual from Groups B and C had specific IgE to uncleaned bean and hull extracts. None of the Group D subjects had specific IgE to these soybean components.

Reactivity to soybean flour and/or dust was demonstrated by specific IgE-RAST and skin prick tests in the 2 bakers investigated for the development of occupational asthma by Levaud *et al* (1994), and in the 4 bakers/confectioners studied by Quirce *et al* (2000).

A positive RAST response against a glycoprotein found in small amounts in all parts of the soybean plant was demonstrated with the sera obtained from 3 residents of Barcelona (Swanson *et al*., 1991). These 3 individuals had experienced asthma-like symptoms after being environmentally exposed to soybean dust.

Morell *et al* (1995) established reactivity to soybean hull and dust extracts via skin prick tests amongst 52/90 and 48/90 respectively of a group of Barcelonian asthmatics treated for acute severe asthma in a major hospital emergency department on an epidemic day. In comparison, only 5/93 and 7/93 asthmatics respectively admitted on a non-epidemic day had a positive skin prick test response.

A positive RAST response to soybean was obtained with the sera of 8/22 exposed shift workers (12 millers and packers, and 10 clerical and maintenance staff; Roodt and Rees, 1995). A positive skin prick test for either full-fat/defatted soybean was also obtained amongst 8 of the 22 total exposed workers. A negative skin prick test was produced with a control group of 20 unexposed workers.

Baur *et al* (1988) studied 140 individuals employed in the baking industry for at least 6 months who were suspected of having occupational asthma and also displayed symptoms of rhinitis and or conjunctivitis. Twenty nine of these workers were RAST-positive to soybean flour. In a related study amongst 14 bakers with reported respiratory symptoms and positive RAST results to the crude extract of soybean flour, specific IgE for soybean lipoxidase and for the lectin were detected in 6 and 3 subjects respectively (Baur *et al*., 1996). Twelve of these 14 bakers had elevated levels of IgE to soybean trypsin inhibitor.

Of 21 cereal workers diagnosed as having occupational asthma, 9 produced a positive skin prick test to soybean flour (Alvarez *et al*.,1996).

Peters (1965) obtained positive results with the asthmatic subject described above following intradermal skin testing using what was described as “soybean allergen”. Two passive transfer tests separated by a 10-month interval also proved positive.

On performing a “direct skin test” on the asthmatic subject described above, Wightman (1938) obtained a “marked” positive response to soybean extract. This same subject also received a series of injections of soybean extract over a 10-month period, and following the fourth injection developed a “moderate local reaction and asthma attack” within 1 hour. A positive passive transfer test was also accomplished using soybean.

A man who reported asthma-like symptoms whilst at work in a soybean mill and at home (situated on one side of the mill) gave positive scratch tests to various products derived from soybean, including the oil (Duke, 1934). An additional 4 individuals employed at the mill who were reported to have “cough and asthma” also gave positive skin scratch test reactions.

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C45: SUBTILISINS

SUMMARY AND CONCLUSION

Information on the potential for subtilisins to cause asthma derives from studies of workers engaged in the manufacture of enzyme-containing detergents and from users of enzyme-containing detergents. The available bronchial challenge data provide sufficient evidence to conclude that subtilisin enzyme preparations can induce occupational asthma. In most cases, positive bronchial challenge results were accompanied by positive skin prick tests and radioallergosorbent tests (RASTs), demonstrating the presence of subtilisin-specific immunoglobulin E (IgE) and indicating that an immunological mechanism underlies subtilisin-induced occupational asthma.

There is sufficient evidence to conclude that subtilisins meet the revised EU criteria (1996) for classification as respiratory sensitisers (causes of asthma).

INTRODUCTION

The subtilisins are protease enzymes derived from Bacillus subtilis strains. These enzymes are mainly used in the manufacture of detergents and animal feeds. Small amounts are also used within the food processing industry for hydrolysis of yeast, gelatin and soya proteins and for leather processing. Subtilisins are not manufactured in the UK but are imported in the form of granulated or liquid preparations containing 0.5 - 10% active enzyme. It is estimated that up to 2500 workers could potentially be exposed to these concentrated preparations. Many thousands of workers will be exposed to detergent preparations and animal feeds containing lower concentrations of active enzymes.

The following information has been summarised from an HSE Risk Assessment Document where a more detailed critical appraisal of the available data can be found (HSE, to be published).

EVIDENCE FOR WORK-RELATED ASTHMA

Franz *et al* (1971) performed non-blinded bronchial challenges with various concentrations of a commercial subtilisin preparation in buffered saline in 10 detergent manufacturing workers with work-related symptoms of asthma. Five control subjects, not further described, were also challenged with the same or more concentrated subtilisins solutions. Immediate reactions (15-45% falls in peak expiratory flow rate, PEFR) were seen in 9/10 workers and in 0/5 controls. In 7 workers the reduction in PEFR was accompanied by wheezing. Five of these 9 subjects were followed for an additional 10 hours and all had a late reaction. All 5 subjects noted the similarity of the work and challenge-related symptoms.

Bernstein (1972) reported results from bronchial and nasal challenge studies with two subtilisin preparations (AlcalaseTM and Amylase ProteaseTM) in 14 domestic and occupational (including laundry and cleaning workers) users of enzyme-containing detergents. In the bronchial challenge studies, subjects inhaled first an aerosol of saline and then, at 10 minute intervals, increasing concentrations of enzyme preparation until a positive response was obtained. In the nasal challenge studies, subjects inhaled saline and then a single dose of enzyme preparation. Of the 7 subjects who underwent bronchial challenge, 6 had an immediate response (5 to AlcalaseTM and 1 to Amylase ProteaseTM) measured as 10-40% reductions in PEFR compared with baseline values. All 7 subjects reported a marked late response between 4-8 hours after challenge and in one subject this was measured as a 75% drop in PEFR. Late measurements were not performed for the other subjects. Five normal and 5 asthmatic controls (asthma not due to enzymes) were also challenged; none reacted. The remaining 7 subjects underwent nasal challenge. All had marked immediate reactions to AlcalaseTM (2) or Amylase ProteaseTM (5), characterised by increased nasal resistance, increased nasal secretions and subjective feelings of difficult nasal breathing. The reactions corresponded to the enzyme product used by the subject. Three normal

controls and 5 with allergic rhinitis not due to enzymes were also challenged and none responded.

Dijkman *et al* (1973) reported results from non-blinded bronchial challenge studies in 6 detergent manufacturing workers with work-related symptoms of wheeze (3/6), breathlessness (5/6) and nasal irritation (4/6) which developed between 1-5 months after first contact with MaxataseTM. Symptoms typically occurred in the evening or at night, and lasted several days or weeks after "heavy" exposure. Five workers showed non-specific bronchial hyperresponsiveness to histamine. All 6 were challenged with saline and nebulised MaxataseTM solution; 4 had an early response to the enzyme and all 6 gave late responses (decreases in forced expiratory volume in one second (FEV_1) and vital capacity (VC) of up to 50%). The late phase reactions were reportedly associated with malaise, headaches, muscle pains and slight fever. In two of these workers, late phase reactions were prolonged, taking 10 hours and 8 days respectively before FEV_1 and VC returned to their pre-challenge levels. An asthmatic with no history of exposure to these enzymes did not react to challenge with the enzyme.

Radermecker and Booz (1970) conducted blinded bronchial challenge tests on two individuals (one detergent manufacturing worker and one housewife) who reported symptoms of asthma related to detergent enzymes (MaxataseTM). The worker was challenged with an aerosol of MaxataseTM in a physiological solution and with the vehicle alone, with a 10-day interval elapsing between each challenge. He showed a dual response to MaxataseTM with a maximal fall in FEV_1 of 70%, but no reaction to the vehicle. No details were provided of the housewife's challenge test, but she was reported to show a "substantial" immediate reaction to MaxataseTM.

Paggiaro *et al* (1984) investigated 6 detergent factory workers who had work-related asthma rhinitis and/or conjunctivitis for between 3 months and 11 years prior to the study. It was reported that hygiene control was "poor" and workers received "considerable exposure" to subtilisin enzymes. Four workers had hyperresponsive airways as assessed by non-specific challenge with "Betanecolo" and in three of these, baseline spirometry revealed moderate bronchoconstriction. Two types of specific bronchial challenge were performed, both likely to have been under non-blinded conditions; inhaling an aerosol of "crude" proteolytic enzyme solution and tipping a detergent powder containing encapsulated (low dust) AlcalaseTM from one tray to another. A 15% or greater decrease in FEV_1 was regarded as a positive result. Five normal and 5 asthmatic controls, not further described, were also tested. All 6 workers reacted to the crude enzyme aerosol, giving 5 immediate and one dual responses. Two reacted to the detergent plus encapsulated AlcalaseTM, with one immediate and one dual response. No control subject reacted to either challenge procedure, even though aerosol doses administered to controls were up to 100 times greater than those administered to symptomatic subjects.

As part of a health evaluation study, single-blind nasal challenge tests were conducted in detergent workers exposed to MaxataseTM and EsperaseTM (Vanhanen *et al*., 2000). Only workers with work-related symptoms and positive skin prick responses to subtilisin were challenged. Of the 76 workers participating in this study (representing 95% of the workforce) 8 met the criteria for nasal challenge. One of these 8 had been diagnosed with occupational asthma and rhinitis due to protease (not further specified) three years earlier and was not challenged. Another worker could not be challenged due to nasal polyposis. Of the remaining 6 workers, 5 gave positive responses to both preparations, while results for the sixth worker were inconclusive.

SUPPORTING DATA

All of the workers described above underwent skin prick tests with the relevant commercial enzyme preparations and, with a few exceptions, positive responses were obtained for those who reacted on bronchial or nasal challenge. In addition, Piaggiaro *et al* (1984) and Vanhanen *et al* (2000) carried out radioallergosorbent tests which demonstrated the presence of subtilisin-specific IgE in workers with subtilisin-induced asthma and rhinitis but not control subjects. This suggests an immunological basis to subtilisin-induced occupational asthma and rhinitis.

Historical health surveillance data from 5 UK detergent manufacturing plants spanning a period of 20 years have been published by Cathcart *et al* (1997). Over this period, 166 cases of occupational asthma thought to be due to enzymes were recorded, 7-39 per year between 1968 and 1974 (total 140), 0-5 cases per year between 1975 and 1980 (total 17) and 0-4 per year after 1980 (total 9). Diagnosis was on the basis of positive skin prick reactions, symptoms and lung function tests. Since subtilisins were the only enzymes used for much of this time it is likely that most of these cases were due to subtilisins, although no specific challenges were performed to confirm this. The decline in cases of occupational asthma coincides with improvements in standards of occupational hygiene within the industry.

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TM denotes registered trade name

SECTION D: The following substances were considered NOT to meet the new EU criteria, revised in 1996, for classification as a respiratory sensitiser (a cause of asthma) and labelling with R42

D1: FORMALDEHYDE

SUMMARY AND CONCLUSION

The available evidence indicates that formaldehyde can bring on the symptoms of asthma in susceptible individuals, probably through irritation of the airways. There is, however, very little convincing evidence that it can induce asthma, given the small number of reported cases in relation to the extent of exposure, and that only a very few of these have proved positive in well-conducted bronchial challenge tests. There is generally little correspondence between the presence of formaldehyde-specific antibodies and the occurrence of asthmatic symptoms in exposed people.

There is not sufficient evidence to conclude that formaldehyde meets the revised EU criteria (1996) for classification as a respiratory sensitiser (a cause of asthma) and labelling with R42.

INTRODUCTION

Formaldehyde as a gas or in aqueous solution (formalin) has a very widespread potential for occupational exposure due to its production and use in a wide variety of products, including foam insulation, plywood and chipboard, textiles, disinfectants and embalming fluids (Bardana *et al*., 1992). It has been estimated that in 1984, 1.3 million workers in the United States were exposed to formaldehyde, approximately one third of them in the medical and health services (Gough *et al*., 1984). In addition, many of the 1.5 million medical and other students in the US are exposed during their training. Non-occupational exposure is ubiquitous due to vehicle exhaust emissions and release from many consumer products, although levels are lower than in the workplace (Smedley, 1996). Formaldehyde is highly water-soluble and experiments in animals show that it dissolves mainly in the upper respiratory tract, before reaching the lungs (Egle, 1972). It has been shown to react with a range of macromolecules of biological importance (Auerbach *et al*., 1977; Feldman *et al*., 1975). Reviews of the toxicology indicate that formaldehyde gas and its aqueous solution are very irritating to the eyes, skin and respiratory system, and solutions can also cause allergic contact dermatitis (Fielder *et al*., 1981; WHO, 1989).

EVIDENCE FOR WORK-RELATED ASTHMA

Although large numbers of workers are potentially exposed to formaldehyde, there are only a small number of reports of occupational asthma related to such exposure available in the literature. In one, Frigas *et al* (1984) studied lung function in 13 patients referred with asthmatic symptoms and who had been exposed to formaldehyde for up to 9 years. Exposure to other chemicals was not addressed in the report. In questionnaires, patients reported coughing, wheezing, nasal congestion, eye irritation and headache to be associated with exposure to formaldehyde; no patients had a previous history of allergic disease. One subject had airways that were hyperresponsive to methacholine. Single- and sometimes double-blind bronchial challenge tests were performed involving inhalation of formaldehyde through a loosely fitting mask. No effects were obtained over the monitoring period of up to 24 hours after the challenge.

Schachter *et al* (1985) performed double-blind bronchial challenge tests on 15 healthy workers routinely exposed to formaldehyde for between 1 to 21 years. None showed hyperresponsiveness to methacholine, and all challenges conducted with formaldehyde were negative.

A single-blind bronchial challenge was conducted in a worker 8 years after he developed occupational asthma associated with formaldehyde; at the time of challenge he had not been exposed for 3 years and had minimal symptoms (Grammer *et al*., 1993). The test was negative.

Hendrick and Lane (1975; 1977) reported respiratory symptoms in nursing staff who sterilised dialysis unit equipment with 35% aqueous formaldehyde. Formaldehyde levels were described as "heavy and prolonged" but were not measured. After joining the unit, 5 of the 28 staff developed recurrent cough accompanied by wheezing that had continued for at least 3 years. Three nurses and a technician with symptoms, and a visitor to the unit who was regularly exposed to formaldehyde and had subsequently developed asthma, underwent bronchial challenge tests wearing nose clips in an attempt to blind the challenge. Responses were seen to formaldehyde in 2 of the nurses, one of whom had pre-existing asthma to house dust mite. The 2 responsive nurses were studied further some years later (Hendrick *et al*., 1982). One had moved away from the unit and no longer had symptoms, the other (who had the house dust mite asthma) worked under improved hygiene conditions in the unit and experienced 5-10 mild asthmatic episodes each year that she associated with night shifts or exposure to formalin spills. Only the nurse still exposed to formaldehyde at work showed a response at bronchial challenge.

Open bronchial challenge tests were performed in 9 people who had complained of adverse health effects from the urea formaldehyde foam insulation used in their homes, and compared the results with those of 9 symptom-free volunteers, some with and some without previous exposures to formaldehyde (Day *et al*., 1984). All of these challenge tests were negative.

A clinic received over a period of 6 years 230 workers presenting with asthmatic symptoms (Nordman *et al*., 1985). All of these patients were reported to have been exposed to formaldehyde. In bronchial challenge tests, only 12 of the 230 patients responded to formaldehyde; only one of these 12 tests was conducted in a blinded manner. There were no responses to placebo. Nine of the 12 responders had hyperresponsive airways, according to the findings of non-specific challenge tests using histamine or methacholine. Of the 218 workers who did not react to formaldehyde, 71 showed non-specific bronchial hyperresponsiveness.

In another study, Burge *et al* (1985) described open bronchial challenge tests on 15 workers presenting with symptoms of occupational asthma following exposure to formaldehyde. Seven reacted to bronchial challenge with formaldehyde, including one only to a very high level. Bronchial hyperresponsiveness was evident in 2 responders and in one non-responsive subject. Ten of the 15 workers were also occupationally exposed to isocyanates, one to a hardwood dust and one to grain, and it is not known whether their asthma could have been induced by these agents. Of these 12 workers with known co-exposures, three reacted to challenge with formaldehyde, and it is uncertain whether formaldehyde had induced their occupational asthma or was triggering asthmatic symptoms in susceptible individuals.

In a study of 8 endoscopy unit and x-ray department staff presenting with symptoms of occupational asthma associated with the use of glutaraldehyde, there was co-exposure to formaldehyde in two cases, one of whom had pre-existing asthma (Gannon *et al*., 1995). Open bronchial challenges were performed with formaldehyde on 7 of the 8 workers. Responses were observed in both of those occupationally exposed to formaldehyde but also in one other. This suggests that cross-reactivity between formaldehyde and glutaraldehyde had occurred.

Bronchial challenges in healthy volunteers have been negative (Sander *et al*., 1986). So too have double-blind challenges in asthmatic volunteers with previously hyperresponsive airways (Sheppard, 1984; Harving *et al*., 1990). Asthmatic subjects without hyperresponsive airways also failed to react to challenge with formaldehyde (Witek *et al*., 1987).

Comparisons of formaldehyde-exposed workers (with or without symptoms) with those not exposed revealed no overall changes in lung function, though one found a slight decrease over a shift in exposed workers (Alexandersson *et al*., 1982; Nunn *et al*., 1990). A pathologist who suffered chest tightness in response to formaldehyde also failed to show lung functional change

after workplace exposure (Kwong *et al*., 1983). Another study, however, found decreased lung function in (mostly) symptomatic workers compared to unexposed controls, though in this case there were no changes in parameters over a working day, week or over a weekend (Schoenberg and Mitchell, 1975). Workers whose exposures had ceased showed no significant differences in lung function or reported symptoms compared to controls.

There are also reports of occupational asthma occurring after exposure to formaldehyde but where clinical investigations have not been carried out (Porter, 1975; Sakula, 1975).

From surveillance data gathered in the UK, 18 cases of asthma were attributed to formaldehyde between 1989 and 1991 (Meredith and McDonald, 1994).

In most of the above worker studies, irritation of the eyes, nose and throat was noted during either challenge testing or while at work (Schoenberg and Mitchell, 1975; Hendrick and Lane, 1977; Alexandersson *et al*., 1982; Kwong *et al*., 1983; Day *et al*., 1984; Frigas *et al*., 1984; Burge *et al*., 1985; Schachter *et al*., 1985). The same has been found in healthy and asthmatic volunteers undergoing bronchial challenge (Saunder *et al*., 1986; Witek *et al*., 1987; Kulle, 1993). Irritation of the upper respiratory tract but no formaldehyde-associated asthma was reported in both a prospective study of pulmonary function conducted on 103 anatomy students exposed to formaldehyde over a 7-month period, and in children exposed to formaldehyde from a school building (Uba *et al*., 1989; Wantke *et al*., 1996). Pharyngeal irritation without asthma has also been brought on by formaldehyde, but the man concerned also reacted to other environmental irritants (Roto and Sala, 1996).

SUPPORTING DATA

Specific immunoglobulin E (IgE) antibodies to formaldehyde-human serum albumin conjugates have only occasionally been found in exposed workers, and even then without any apparent correlation with respiratory symptoms (Patterson *et al*., 1986; Kramps *et al*., 1989; Grammar *et al*., 1993 . They have also been found in children exposed to formaldehyde from a school building, although none had asthma (Wantke *et al*., 1996). Other studies have failed to find such antibodies (Nordman *et al*., 1985; Patterson *et al*., 1986; Thrasher *et al*., 1987; Kramps *et al*., 1989; Grammer *et al*., 1990). Specific IgG antibodies to the same conjugate have likewise been found in some groups of exposed people, but not others (Thrasher *et al*., 1987; Grammer *et al*., 1990; Grammer *et al*., 1993).

No internationally-validated animal tests are currently available that allow prediction of the ability of a chemical to induce asthma in man. The findings of the investigations that have been conducted, in guinea pigs (Lee *et al*., 1984) and mice (Potter and Wederbrand, 1995), were negative.

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D2: HYDRALAZINE

SUMMARY AND CONCLUSION

Only one case of occupational asthma associated with hydralazine has been reported. Although a direct pharmacological mechanism of action can be postulated, this one case has to be considered in the context of widespread manufacture and use of the drug.

There is not sufficient evidence to conclude that hydralazine meets the revised EU criteria (1996) for classification as a respiratory sensitiser (a cause of asthma) and labelling with R42.

INTRODUCTION

Hydralazine hydrochloride is a widely-used drug which reduces peripheral resistance and blood pressure as a result of a direct vasodilatory effect on vascular smooth muscle. Its mechanism of pharmacological action is uncertain, although it is thought by some researchers to owe its activity to biotransformation to nitric oxide *in vivo*. Some patients treated with hydralazine develop a drug-induced systemic lupus erythematosus with antibodies to both hydralazine and DNA (AHFS, 1991; Bhandare *et al*., 1992; Smith, 1992).

EVIDENCE FOR WORK-RELATED ASTHMA

There is only one report of occupational asthma, which was associated with periodic exposure of an operator to hydralazine in a pharmaceutical plant (Perrin *et al*., 1990). This male worker had a history of seasonal rhinitis, but was negative in skin prick and specific immunoglobulin E (IgE) tests for common allergens. He had previously experienced asthmatic symptoms while working with psyllium, although the cause of this was unclear since he failed to react to psyllium at bronchial challenge and was negative in skin prick and specific IgE tests. He did, however, give a response to methacholine that was in the asthmatic range. Three years after changing from working with psyllium to hydralazine he again developed asthmatic symptoms, which were investigated a year later. At this time he again registered in the asthmatic range on response to challenge with methacholine (responsiveness in the interim years had apparently not been measured).

A skin prick test and specific IgE and IgG to hydralazine were negative. Total IgE was normal. Bronchial challenge testing was carried out on different days with lactose and twice with hydralazine powder (7 and 30 minute exposures), during which particle concentrations were kept below 10 mg/m^3. The test was not blinded, and normal or asthmatic controls were not included. No effect was seen with either lactose or 7 minutes of hydralazine, whereas the 30 minute exposure induced a late response with a maximum fall of 35% in the forced expiratory volume in one second.

In conclusion, this man was clearly susceptible to developing asthma, firstly to psyllium and subsequently to hydralazine. The mechanism underlying the asthma is unclear, but there was no evidence of an immunological reaction to hydralazine. It is possible that the pharmacological activity of hydralazine is mediated by the release of nitric oxide, which inhibits cholinergic neurotransmission in the airways, so that hydralazine would be likely to induce bronchial relaxation rather than constriction (Sorkness *et al*., 1993). However, there is speculation that raised levels of nitric oxide may enhance the immunological response involved in the development and prolongation of asthma (Barnes and Liew 1995).

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D3: METHYL METHACRYLATE

SUMMARY AND CONCLUSION

Several cases of asthma associated with exposure to methyl methacrylate have been reported. These appear to be associated with “end-user” occupations where the pattern of exposure is characterised by high peak levels of short duration, and it seems likely that they represent asthmatic responses triggered by irritation of the respiratory tract. For some cases, exposure to substances other than methyl methacrylate was possible. Overall, there is no good evidence that methyl methacrylate is able to produce a hypersensitive state in the airways.

There is not sufficient evidence to conclude that methyl methacrylate meets the revised EU criteria (1996) for classification as a respiratory sensitiser (a cause of asthma) and labelling with R42.

INTRODUCTION

Methyl methacrylate monomer is principally used in the manufacture of cast acrylic sheet. Other uses include resins and surface coatings, moulded and extruded products, manufacture of multifunctional methacrylates and medical and dental applications.

The following information has been summarised from an HSE Criteria Document for an Occupational Exposure Limit, where a more detailed critical appraisal of the available data can be found (Cary *et al*., 1995).

EVIDENCE FOR WORK-RELATED ASTHMA

Three cases of asthmatic responses associated with occupational exposure to methyl methacrylate were investigated by bronchial challenge involving simulation of occupational conditions (Savonius *et al*., 1993). Each individual was also challenged with a placebo or other “inert compounds” found in the workplace. Challenge under the simulated occupational conditions resulted in a reduced peak expiratory flow of 15-26% compared to the appropriate control levels, with responses being either late or dual (i.e. early and late). Exposure concentrations, which were not measured, were likely to have been transiently high, as indicated in the study by Pickering *et al*., 1986, and it is not known whether such exposures would have triggered respiratory reactions in control subjects, particularly asthmatic individuals. Also, there is the possibility that exposure to substances other than methyl methacrylate may have occurred in the workplace, judging from the nature of the procedures involved, but this was not addressed in the report. Overall, no firm conclusions can be drawn regarding the potential of methyl methacrylate to induce asthma in exposed workers.

In one case report respiratory symptoms were clearly related to occupational exposure (Pickering *et al*., 1986). A bronchial challenge test was conducted simulating occupational conditions, and an asthmatic reaction was recorded at 6 hours. In this test, methyl methacrylate concentrations reached 374 ppm; on repeating the procedure in a fume cupboard a maximum level of 76 ppm was recorded, and there was no response under these conditions. For this individual, the appearance of asthmatic symptoms was considered to be due to exposure to brief, high levels of methyl methacrylate vapour, but no conclusions are possible regarding production of the hypersensitive state.

In another case study, for which only limited experimental detail was reported, the interpretation of findings indicative of occupational asthma was confounded by the subject’s reactivity towards gentamycin (Reynaud-Gaubert *et al*., 1991). No firm conclusions could be drawn in regard to methyl methacrylate.

Two further cases of asthma in connection with methyl methacrylate exposure have been reported (Lozewicz *et al*., 1985). For one subject, a challenge test resulted in an immediate response, although the exposure concentrations were not reported, and it is uncertain whether or not the reaction was specific to the methacrylate. The second case was not clearly occupationally-related; no asthmatic reaction was obtained following challenge with methyl methacrylate. Again, no useful conclusions can be drawn from these results.

In a study reported as an abstract, the results of a questionnaire indicated some exacerbation of pre-existing asthma due to methyl methacrylate exposure, although subsequent spirometry tests did not reveal any impairment of respiratory function (Andrews *et al*., 1979).

SUPPORTING DATA

No useful immunological or other supporting data are available.

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D4: DIETHYLAMINOETHANOL

SUMMARY AND CONCLUSION

The only report of diethylaminoethanol associated with asthmatic symptoms is consistent more with reactive airways dysfunction syndrome than with conventional occupational asthma.

There is not sufficient evidence to conclude that diethylaminoethanol meets with the revised EU criteria (1996) for classification as a respiratory sensitiser (a cause of asthma) and labelling with R42.

INTRODUCTION

Diethylaminoethanol is widely used in industry to counter corrosion in humidifiers and water-based steam heating systems. It is also used as a chemical reagent. The vapour is irritating to respiratory tract and eyes, and the liquid is an eye irritant. It has also been reported to cause dermatitis (Toren, 1994).

EVIDENCE FOR WORK-RELATED ASTHMA

The only report of diethylaminoethanol causing asthmatic symptoms describes a leak of steam containing it into the ventilation system of a large office block (Gadon *et al*., 1994). Many of the 2500 workers in the block complained of symptoms indicating irritation of the respiratory tract, nose and throat, and 49 required hospital treatment. Airborne levels of diethylaminoethanol during the leak were not measured, but were not considered to be high when monitoring started three days later.

Fourteen workers reported developing asthma for the first time following the leak, including 11 within two weeks of the incident. The most common complaint was of work-related cough, but other symptoms including wheezing, shortness of breath and chest tightness were also reported. It was not stated whether any of the 14 were among those attending hospital immediately following the leak, but in any case they were subject to clinical investigations carried out 6 to 7 weeks later. The findings are not always clear, but it seems that 7 cases were ‘confirmed’ as having asthma, largely on the basis of work-related peak flow changes (6/7) or airways being hyperresponsive to methacholine together with work-related symptoms (1/7), and 7 were described as ‘suspect’. Spirometric pulmonary function tests carried out in 12 of the subjects revealed obstructive airways disease in 2 ‘confirmed’ and 2 ‘suspect’ cases.

The occurrence of work-related peak flow changed 6 to 7 weeks after the leak, when diethylaminoethanol levels would be expected to be very low if present at all, suggests that the workers who had developed asthma were then reacting to some other factor in the office environment. No bronchial challenge testing was carried out to try to clarify the situation. The authors of the study also indicate that psychological factors may have been involved in some of the observations.

Overall, this single report does not provide good evidence that diethylaminoethanol caused conventional occupational asthma, given that no specific bronchial challenges were carried out and that decreases in peak flows were obtained in the apparent absence of diethylaminoethanol. Instead, the evidence indicates that these workers may have developed reactive airways dysfunction syndrome, a well-documented asthma-like condition often resulting from accidental inhalation of a high concentration of an irritant vapour (Brooks, 1995). The syndrome is outside the scope of the revised EU criteria (1996) for classification as a respiratory sensitiser (a cause of asthma) and labelling with R42.

SUPPORTING DATA

There are no supporting data.

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D5: DIMETHYLAMINOETHANOL

SUMMARY AND CONCLUSION

Despite significant industrial use of dimethylaminoethanol, only one good case of occupational asthma apparently arising from exposure to dimethylaminoethanol has been reported. The underlying mechanism for any induction of asthma is uncertain.

There is not sufficient evidence to conclude that dimethylaminoethanol meets the revised DU criteria (1996) for classification as a respiratory sensitiser (a cause of asthma) and labelling with R42.

INTRODUCTION

The major use of dimethylaminoethanol is in the manufacture of organic flocculants. In the UK, approximately 800 people are regularly exposed during its manufacture and use, with many thousands being occasionally exposed. The liquid is a skin and eye irritant, and the vapour is irritating to the eyes and upper respiratory tract (Davies *et al*., 1997).

The following information has been summarised from an HSE Risk Assessment Document, where a more detailed critical appraisal of the available data can be found (Davies *et al*., 1997).

EVIDENCE FOR WORK-RELATED ASTHMA

There is a report of the development of occupational asthma in a spray painter, apparently in association with the use of a paint containing 2% dimethylaminoethanol (Vallieres *et al*.,(1977). The subject had no previous history of asthma, other respiratory disease, rhinitis or allergy. Work-related decreases in peak flow were found. Specific bronchial challenges were carried out with a control solution, and the paint and its constituents. It is unclear whether or not these tests were performed in a blinded manner. Only challenges with solutions containing dimethylaminoethanol were positive in the patient, although it is unclear whether these tests were performed in a blinded manner. Two control subjects, one of whom was asthmatic, failed to react. Non-specific hyperresponsiveness to histamine increased in the patient but not the controls. Overall, this appears to be a clear case of dimethylaminoethanol-induced asthma in one individual.

An investigation was conducted at a can-manufacturing plant that had started using a water-based epoxy spray containing 2% dimethylaminoethanol (Gann and Roseman, 1984). Three months after introduction of the spray, a mechanic servicing the spray-liner developed symptoms of chest constriction, shortness of breath, cough and a skin rash. Pulmonary function tests revealed decreased forced expiratory volume in on second (FEV 1) and forced vital capacity (FVC), and symptoms worsened on exposure to the new spray at work. In order to investigate this further, a bronchial challenge test to 2% dimethylaminoethanol only was conducted, although whether this was open or blinded is not clear from the report. A delayed reaction characterised by a reduction in both FEV 1 and FVC was noted, together with symptoms of chest tightness, skin rash and an elevated temperature. Overall, this study does not provide good evidence that dimethylaminoethanol induced asthma in the subject. Instead, the findings suggested a pattern of restrictive lung damage or perhaps allergic alveolitis, exacerbated by exposure to irritant dimethylaminoethanol.

A follow-up investigation was conducted at this plant a year later (Gann and Roseman, 1984). Fourteen employees exposed to dimethylaminoethanol were compared with 4 workers who acted as unexposed controls. Lower respiratory tract symptoms (cough, wheezing or shortness of breath) had been reported by 11 of the 14 during the previous year, although for three of them this was before the introduction of the new spray. The controls had no such symptoms. Pulmonary function testing conducted on the 14 dimethylaminoethanol-exposed workers before and after a shift showed no significant reduction in performance. No significant decreases in peak

flow were measured amongst six symptomatic workers exposed to dimethylaminoethanol who were provided with peak flow meters. Thus the presence of occupational asthma was not confirmed in this study.

A study is available in abstract form only in which two subjects received bronchial challenge tests to investigate the possible development of occupational asthma arising from exposure to dimethylaminoethanol and hexamethyl diisocyanate, present as hardeners in paints (Cockcroft *et al*., 1979). Positive responses were produced in both of the painters. However, due to the limited nature of reporting, no conclusions can be drawn from this study regarding the potential for dimethylaminoethanol to induce asthma.

SUPPORTING DATA

Skin prick testing with dimethylaminoethanol has generally been negative or the interpretation complicated by irritant responses (Vallieres *et al*., 1977). In one study, 48 workers exposed to dimethylaminoethanol were given unspecified skin tests (Pokrovskaya *et al*., 1986). Seven of the subjects were reported to have been “sensitised” to dimethylaminoethanol, but no details were given, and the generally poor reporting of this study precludes any conclusions being drawn.

No specific immunoglobulin E antibody to dimethylaminoethanol has been detected, other than in a study where an apparently unexposed control was also positive (Vallieres *et al*.,1977; Gann and Roseman, 1984). No specific immunoglobulin G has been detected (Gann and Roseman, 1984).

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D6: ETHANOLAMINE

SUMMARY AND CONCLUSION

In contrast to the widespread use of ethanolamine, the number of reports of occupational asthma is small, and the findings of the studies that are available do not provide good evidence that ethanolamine can induce occupational asthma.

There is not sufficient evidence to conclude that ethanolamine meets the revised EU critieria (1996) for classification as a respiratory sensitiser (a cause of asthma) and labelling with R42.

INTRODUCTION

Ethanolamine is widely used in industry and is produced high tonnage. It is also used extensively in cosmetics such as hair care products. It is irritating to the skin and eyes, and has been reported to cause pulmonary irritation after repeated exposure (Binks *et al*., 1992).

EVIDENCE FOR WORK-RELATED ASTHMA

A cleaner who was exposed over many years to several cleaning products developed cough and fever on using a particular type of detergent which contained ethanolamine amongst other ingredients (Savonius *et al*., 1994). She underwent bronchial challenge testing with the detergent, and gave a positive immediate response and subsequent fever. A control exposure and another detergent were negative at challenge. She was not challenged with ethanolamine, and these findings do not provide good evidence that ethanolamine was the cause of the response. It is not even clear that this subject had occupational asthma, since the fever suggests some form of pneumonitis.

In an earlier report, 14 users of ‘beauty culture products’ were described as having asthma, rhinitis or conjunctivitis (Gelfand, 1963). Al were atopic and apparently had multiple allergies to chemicals. Ten of the patients with asthmatic symptoms relating to handling the products apparently gave positive bronchial challenge tests to both ethanolamine and ammonium thioglycolate. Asthmatic and non-asthmatic control subjects failed to react at challenge. However, the confusing and incomplete reporting of this study, in patients with apparently multiple allergies, makes it difficult to interpret the results and draw any conclusions regarding ethanolamine.

Two cases of occupational asthma attributed to ethanolamine were reported in the UK under the Surveillance of Work-related and Occupational Respiratory Disease scheme in 1993 (Sallie *et al*., 1994). Also, Butcher (1982) includes in a review unreferenced data indicating that ethanolamine gas given a positive, immediate, bronchial challenge reaction but that the mechanism is uncertain. In the absence of more information regarding these cases, no conclusions can be drawn.

SUPPORTING DATA

In a study described above, 13 out of the 14 patients gave some reaction to intradermal testing with ethanolamine (Gelfand, 1963). However, it is not possible to determine if these were allergic or irritant reactions, and most of the subjects also tested positive to two other chemicals, ethylenediamine and ammonium thioglycolate.

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D7: METABISULPHITE

SUMMARY AND CONCLUSION

There is only one well-documented case of occupational asthma associated with the use of metabisulphite, despite widespread use of this chemical in industrial and amateur situations. The occurrence of allergy to ingested metabisulphite , with or without the presence of asthma, indicates that sensitisation can occur by the oral route.

There is not sufficient evidence to conclude that metabisulphite meets the revised EU criteria (1996) for classification as a respiratory sensitiser (a cause of asthma) and labelling with R42.

INTRODUCTION

Metabisulphite as the sodium or potassium salt has a wide variety of uses including chemical and photoprocessing, in the textile, dyestuff and tanning industries, in water treatment works, and as a food and beverage preservative. It is also widely used in amateur wine and beer making. It is a respiratory irritant, causing broncho-constriction in people who are already asthmatic, and is extensively used to study airway hyperresponsiveness. At higher doses it can cause similar reactions in non-asthmatics. The characteristics of these responses suggest that they are due to the effect of inhaled sulphur dioxide liberated from metabisulphite (Wright *et al*., 1990; IARC, 1992; Nannini and Hofer, 1997).

EVIDENCE FOR WORK-RELATED ASTHMA

There is only one well-documented case of occupational asthma associated with the use of metabisulphite . A man who used sodium metabisulphite powder at work developed conjunctivitis, rhinitis and asthma after a latent period of about 4 weeks (Malo *et al*., 1995). He had no previous history of asthma, did not have bronchial hyperresponsiveness, and gave negative skin prick tests to common allergens and to metabisulphite . He underwent bronchial challenge with metabisulphite either as a powder mixed with lactose, or as a solution (diluent not stated). It was not clear if the challenge was conducted in a blinded manner. On challenge there were substantial falls in forced expiratory volume in one second at concentrations of metabisulphite well below levels that have caused an irritant reaction in asthmatic subjects. He did not react to lactose, and a normal control subject failed to react to the metabisulphite.

A photographic technician developed asthma and worsening of pre-existing eczema 2 years after starting work in a processing laboratory (Jacobs and Rycroft, 1995). She gave a positive skin patch test with sodium metabisulphite, indicating that an allergy to metabisulphite aggravated her eczema, but the cause of her asthma remained uncertain.

Three other cases of occupational asthma ascribed to metabisulphite have been very briefly reported, but not further details are available (ACGIH, 1991; Sallie *et al*., 1994).

SUPPORTING DATA

There are several reports of people developing allergies following ingestion of foods and drinks containing metabisulphite (for example, Yang *et al*., 1986: Sokol and Hydick, 1990; Hein *et al*., 1996; Miltgen *et al*., 1996). The allergic condition may be manifested as anaphylaxis, angio-oedema, urticaria and/or asthma. Only one study has included bronchial challenge, when a female subject gave a positive reaction to low concentrations of metabisulphite in an apparently unblended test (Jamieson *et al*.,1985). However, the severity of her asthma may have influenced the reaction to the metabisulphite. Although this woman failed to react to a skin-prick test with metabisulphite, investigation of other patients have indicated that at least some reactions following oral exposure to metabisulphite are immunoglobulin E medicated (Yang *et al*., 1986; Sokol and Hydick, 1990).

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D8: STYRENE

SUMMARY AND CONCLUSION

Despite widespread industrial exposure to styrene, there are only a few published cases of asthma in which it is implicated, and in each case the evidence of a role for styrene in inducing the asthma is not convincing.

There is not sufficient evidence to conclude that styrene meets the revised EU criteria (1996) for classification as a respiratory sensitiser (a cause of asthma) and labelling with R42.

INTRODUCTION

Styrene is a high production volume chemical used in the manufacture of glass-reinforced plastics, resins and synthetic rubber, and many thousands of workers are exposed to it in the European Union (Welp *et al*., 1996).

EVIDENCE FOR WORK-RELATED ASTHMA

A cohort of 35,443 men and women employed in 660 European factories who were exposed to styrene during the manufacture of reinforced plastic products was assessed for causes of mortality compared to national reference rates (Welp *et al*., 1996). Mortality from asthma was not associated with styrene exposure. While this finding does not provide evidence that styrene cannot induce asthma, it does show that in the large number of people exposed it did not cause disease severe enough to result in excess mortality.

A technician who was exposed to cobalt octoate and styrene developed occupational asthma, with convincing work-related falls in peak flow measurements (Hayes *et al*., 1991). He underwent single-blind bronchial challenge testing with a control solution (white spirit), styrene alone and cobalt octoate in styrene, but not to cobalt octoate alone. There were strong dual asthmatic reactions to styrene alone and to styrene combined with cobalt octoate, but not to the control exposure. The co-exposure to cobalt, which is known to be able to cause asthma, makes interpretation of these findings difficult, and it is not possible to draw a firm conclusion that styrene induced the asthma in this case.

Moscato and colleagues have reported three cases of occupational asthma and one of rhinitis associated with working with styrene (Moscato *et al*., 1987; Moscato *et al*., 1988). The first two workers were exposed to both styrene and ethylbenzene at work; both suffered from work-related asthma and one a work-related rash. Both underwent apparently unblended bronchial challenge testing with ethylbenzene and with styrene at a reportedly non-irritant concentration. Both gave immediate asthmatic responses to styrene but not ethylbenzene, and the man with a history of work-related rash developed a widespread urticarial rash 24 hours after the challenge. The third person was exposed to various resins, pigments and solvents including styrene, and developed asthma 19 years after starting work. He was challenged in an apparently unblended manner with various substances, including phthalic anhydride, epoxy resin and styrene. Only styrene proved positive, producing a dual reaction. Finally, the subject with work-related rhinitis underwent nasal challenge with styrene and acetone, giving a positive reaction with the former but not the latter. Overall, these studies do not provide good evidence that styrene can induce asthma. The immediate reactions in the first tow cases may have been irritant effects, while any conclusion is also uncertain with the third subject, due to the multiple exposures and long latent period.

There is also the case of a woman who developed rhinitis and occasional attacks of dyspnoea around the time that a factory opened close to her home; she had no previous history of allergy (Candura *et al*., 1993). There was no mention of a latent period. Since the factory used styrene, she was given apparently unblended bronchial challenge tests with styrene and a control substance; both proved negative. The apparent lack of latent period and the negative bronchial

challenge indicate that this woman's asthma was not induced by styrene. However, a nasal challenge was positive with styrene, so that it may have been involved in the development of the rhinitis.

One case of occupational asthma attributed to styrene was reported in the UK under the Surveillance of Work-related and Occupational Respiratory Disease scheme in 1993 (Saillie *et al*., 1994). In the absence of more information, no conclusions can be drawn about this single case.

SUPPORTING DATA

Specific immunoglobulin E to styrene, measured by radioallergosorbent test, was not detected in one styrene worker with asthma or another with rhinitis (Moscata *et al*., 1988).

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D9: ACETIC ANHYDRIDE

SUMMARY AND CONCLUSION

Acetic anhydride has structural similarity to phthalic, trimellitic, and maleic anhydrides, which are considered to be capable of producing occupational asthma. However, in the absence of any positive evidence for asthma development with acetic anhydride, and in view of mechanistic arguments suggesting that unlike these other anhydrides acetic anhydride would not possess sensitising properties, it can be concluded that acetic anhydride would not be capable of causing occupational asthma.

There is not sufficient evidence to conclude that acetic anhydride meets the revised EU criteria (1996) for classification as a respiratory sensitiser (a cause of asthma) and labelling with R42.

INTRODUCTION

Acetic anhydride is a key raw material in several significant industrial products and is also used in laboratory analysis work. It is supplied as a liquid at 98% concentration with 2% acetic acid, with approximately 190 000 tonnes/year being used by UK industry.

The following information has been obtained from an HSE Risk Assessment Document, where further discussion of the toxicity of acetic anhydride can be found (HSE, to be published).

EVIDENCE FOR WORK-RELATED ASTHMA

No information relating to occupational asthma is available.

SUPPORTING DATA

No data of relevance to occupational asthma are available from animal studies. In view of the lack of direct evidence on this endpoint, consideration has been given to the likely mechanism of asthma induction by other anhydrides such as phthalic, trimellitic and maleic anhydride, and whether the chemical structure of acetic anhydride is consistent with the potential for similar mechanisms to operate.

Phthalic, trimellitic and maleic anhydrides are cyclic in structure, and are capable of cross-linking with tissue proteins. The resultant antigenic complexes are capable of stimulating antibody formation, for example, as evidenced by the existence of IgE antibodies directed against trimellitic anhydride conjugated to human serum albumin in workers. This suggests that the mechanism of asthma induction with the cyclic anhydrides might well be immunologically mediated.

In contrast, acetic anhydride lacks a cyclic structure, and although theoretically capable of binding to tissue proteins, cross-linking could not occur, and it is uncertain whether any resulting hapten would be capable of stimulating antibody formation. This is because any hapten would only consist of a 2-carbon (acetyl) fragment, which due to its small size would be unlikely to provoke an antibody response.

These considerations suggest significant differences in the potential to elicit immunological responses between acetic anhydride and the cyclic anhydrides. Overall, in the absence of any positive evidence for asthma development with acetic anhydride, and the mechanistic argument suggesting acetic anhydride would not possess sensitising properties, it is postulated that acetic anhydride would not be capable of causing occupational asthma.

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D10: CYANOACRYLATES

SUMMARY AND CONCLUSION

The body of evidence for the induction of asthma by cyanoacrylates is small in comparison to the extent of exposure to them occupationally and in the home. There is only one report of asthma that can clearly be associated with exposure to methyl cyanoacrylate. Although there are a number of case reports indicating asthmatic reactions to ethyl cyanoacrylate and ethyl cyanoacrylate-based adhesives, very few of them provide a profile of information that is convincing evidence for induction of asthma. For instance, the bronchial challenge tests that are available have generally not been conducted using stringent protocols.

There is not sufficient evidence to conclude that methyl cyanoacrylate and ethyl cyanoacrylate meet the revised EU criteria (1996) for classification as a respiratory sensitiser (a cause of asthma) and labelling with R42.

INTRODUCTION

There is extensive use of cyanoacrylate-based adhesives, not only for a wide range of industrial applications but also as household products. Most of the commercially available adhesives are likely to be based on ethyl cyanoacrylate and to a lesser extent methyl cyanoacrylate, although other cyanocrylates (such as isobutyl, amyl and heptyl) have been marketed. Thus it seems reasonable to assume that there is the potential for a substantial number of people to be exposed to ethyl or methyl cyanoacrylates, either at work or at home.

The following information has been summarised from an HSE Risk Assessment Document, where a more detailed critical appraisal of the available data can be found (HSE, 2000).

EVIDENCE FOR WORK-RELATED ASTHMA

Most of the useful information relating to cyanoacrylate-induced asthma is in the form of case reports (e.g. Kopp *et al*., 1985; Lozewicz *et al*., 1985; Nakazawa, 1990; Savonius *et al*., 1993), supplemented by a small number of workplace surveys (e.g. London and Lee, 1986; Trottier *et al*., 1994). In interpreting the findings of these studies, there are difficulties in that control subjects were often not used for those that included bronchial challenge tests, so that there was no clear indication of whether or not the exposure concentrations involved would have caused irritant responses in healthy people. Indeed, in some studies concentrations used for the bronchial challenge tests are clearly high and probably irritant even for non-asthmatic subjects. For some reports there is also uncertainty about whether or not the adhesive could have induced the state of asthma, particularly when reactions appeared to develop after latent periods of only 2-4 weeks from starting work with the adhesive.

The records of the Surveillance of Work-related and Occupational Respiratory Disease scheme for 1989-1998 reveal about 5 new cases of asthma per year, from a very disparate range of types of employment (e.g. police, car assembly, lampshade manufacture, gas pipe manufacture, boat repair), in relation to "cyanoacrylate adhesive". Not all reports reliably identify the substance; some report 'glue' or various adhesive brand names. In 1994 there was an unusually high rate of 12 cases reported.

SUPPORTING DATA

Very little additional information is available. In one study, skin prick tests were performed using a “cyanoacrylate”- human serum albumin conjugate, and no skin responses were obtained (Savonius *et al*., 1993). However, it is unclear whether the conjugate used in these tests was an appropriate antigenic material.

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D11: GUAR GUM

SUMMARY AND CONCLUSION

In contrast to the widespread use of guar gum, the number of reports of occupational asthma is small, with most if not all apparently coming from a single research team. It also seems that some of the subjects involved may have been included in more than one paper, leading to double counting. Thus although the findings of the studies are suggestive of an asthmatic effect with an immunological basis, the number of reported cases is small in relation to the extent of exposure.

There is not sufficient evidence to conclude that guar gum meets the revised EU criteria (1996) for classification as a respiratory sensitiser (a cause of asthma) and labelling with R42.

INTRODUCTION

Guar gum is a high molecular weight carbohydrate commercially obtained from guar plants (*Cyamopsis psoraloides, Cyamopsis tetragonoloba*), a vegetable found in tropical and subtropical regions of the world. It has widespread and varied uses, including in foods, cosmetics, pharmaceuticals, paper manufacture, textiles, carpet manufacture (to adhere dye to fibre), printing, polishing, and as a thickener and emulsifier (Kanerva *et al*., 1988; Malo *et al*., 1990).

EVIDENCE FOR WORK-RELATED ASTHMA

In an evaluation of occupational asthma and immunological sensitisation to guar gum in which 162/177 (92%) of employees at a carpet manufacturing plant participated, 5 individuals were identified who had a history suggestive of occupational asthma, a positive skin reaction to guar gum and nonspecific bronchial hyperresponsiveness to methacholine (Malo *et al*., 1990). Four of these 5 underwent specific bronchial challenges to either lactose or guar gum (although it is not clear if these were blinded), whilst the fifth individual who met the criteria did not undergo specific challenge due to a history of severe bronchospastic reaction on exposure to guar gum and a forced expiratory volume in one second (FEV_1) of only 1.6l. Two of the 4 individuals given challenges showed a steep fall in FEV_1 immediately after the guar gum exposure, while the other 2 gave negative responses. Overall, based on the tests conducted occupational asthma was confirmed in 2 subjects and considered to be highly probable in the subject not tested.

Occupational asthma caused by guar gum was diagnosed in 3 individuals, 2 involved in carpet manufacturing, the other in pharmaceutical preparation (Lagier *et al*., 1990). The 3 subjects (but no controls) were given single-blind bronchial challenge tests to either lactose or guar gum. Immediate marked decreases in FEV_1 were observed with guar gum in all 3 individuals, with one individual showing a dual reaction. There was no response to the lactose administration. A nonspecific challenge test with histamine conducted the following day demonstrated bronchial hyperresponsiveness in all three subjects. In the individual working in the pharmaceutical industry, peak expiratory flow rate (PEFR) was measured for 4 weeks at work and including weekends. Changes in PEFR at or above 20% were recorded on two occasions, one following exposure to guar gum, the other in relation to exposure to a cat away from work. It should also be noted that this individual was considered in a previous paper to have occupational asthma to the pharmaceutical being produced (penicillamine), as well as the guar gum used in the casing (Lagier *et al*., 1989, and therefore there may be some doubt as to the cause of the change in PEFR. It is stated in another paper (Malo *et al*., 1990) that one of these individuals was also included in the carpet factory survey above, although from the data provided it is not clear which one.

In two studies testing and validating new exposure methodology, 3 and 4 individuals respectively with a history stated to be suggestive of occupational asthma (to guar gum) were exposed to aerosolised guar gum (Cloutier *et al*., 1989; Cloutier *et al*., 1992). Falls in FEV_1 greater than 20% were recorded with all 7 individuals from both studies following exposure times of up to 4.5

minutes. From the limited personal data available in these papers it is not clear if these subjects had been included in other papers published by this research team.

Three workers previously exposed to guar gum from unstated sources, and who had shown a positive response to bronchial challenge, were rechallenged 2 or more years later following removal from exposure to guar gum, to evaluate any change in specific bronchial responsiveness (Lemière *et al*., 1996). Only one of the individuals showed a reduction in such responsiveness. From the limited personal data available in this paper it is not clear if these individuals had been included in other papers published by this research team.

Rhinitis (but not asthma) was reported in 3 individuals with between 1-2 years exposure to fine guar gum powder, 2 from its use as an insulator in rubber cables, the other exposed to guar gum in the paper industry (Kanerva *et al*., 1988). In the 2 individuals in the power cable laboratory, positive results were obtained in nasal challenge tests. When guar gum was identified as the causative agent in the power cable laboratory, it was replaced and the rhinitis of the workers stopped. The paper worker was also positive in a nasal challenge test, but when use of guar gum was phased out, he continued to have rhinitis from non-specific dusts. This paper also reported that a fourth person exposed to guar gum from paper handling, examined in 1974, had a pattern of symptoms indicative of rhinitis in response to the exposure, but as she could not be re-examined it was not possible to confirm this diagnosis.

After 2 years being occupationally exposed to guar gum during the mixing of pet foods, a worker complained of an increasingly distressing cough which did not respond to cough suppressants or bronchodilators, along with tearing, irritated eyes, nasal obstruction and rhinorrhea (Leznoff *et al*., 1986). Pulmonary function and histamine challenge tests were normal, but within 10 minutes of starting a 30-minute challenge to guar gum, the subject developed sneezing, rhinorrhea, nasal obstruction and gross conjunctival inflammation. After a further 24 hours the exposure was repeated, with the same effects noted. On subsequent return to work the cough, rhinitis, conjunctivitis, snoring and fitful sleeping returned. Having quit his job the respiratory symptoms subsided within a week, although he did develop oedema of the lips following eating ice cream containing guar gum, and a similar response was obtained by oral challenge with pure guar gum. No reaction was obtained with ice cream not containing guar gum.

SUPPORTING DATA

Specific immunoglobulin E (IgE) to guar gum has been found in a number of cases, often correlating with asthma, rhinitis or positive bronchial challenge tests (Kanerva *et al*., 1988; Lagier *et al*., 1990; Malo *et al*., 1990; Lemière *et al*., 1996).

Skin prick tests have often been positive, correlating with asthma, rhinitis or positive bronchial challenge findings (Leznoff *et al*., 1986; Kanerva *et al*., 1988; Lagier *et al*., 1990; Lemière *et al*., 1996).

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D12: SENNA

SUMMARY AND CONCLUSION

Although two individual cases of suspected occupational asthma following exposure to senna have been reported, there are deficiencies in the conduct of the bronchial challenges such that the findings do not provide good evidence that senna can actually induce asthma.

There is not sufficient evidence to conclude that senna meets the revised EU criteria (1996) for classification as a respiratory sensitiser (a cause of asthma) and labelling with R42.

INTRODUCTION

Senna preparations are derived from the dried leaves or pods of *Cassia senna* or C.*angustifolia*. Senna is an anthraquinone- based laxative used in tablet, granule or syrup form (Martindale, 1996).

EVIDENCE FOR WORK-RELATED ASTHMA

A male factory worker with a history of rhinoconjunctivitis developed progressive rhinitis, itchy eyes and dyspnoea when mixing powdered henna and senna used in hair dyes (Helin and Makinen-Kiljunen, 1996). No symptoms were experienced outside the work environment. In a histamine challenge test mild bronchial hyperresponsiveness was observed. Following bronchial challenge with senna powder a fall in forced expiratory volume in one second (FEV_1) of 23% was observed immediately after exposure, and a fall of 33% after 20 minutes. However, no firm conclusions can be drawn from these findings, given the lack of a challenge with a control substance. No control subjects were challenged with 0SENNA and the patient was not tested with henna, so that it is possible that the asthmatic symptoms were caused by exposure to henna rather than senna.

A male maintenance worker with suspected occupational asthma experienced a range of symptoms, comprising sneezing, rhinitis, nasal breathing difficulties, dyspnoea and an audible wheezing, while working in areas where laxative tablets and teas were prepared in a factory (Baur and Luderschmidt, 1983). He had previously experienced episodes of dyspnoea when using two-pack paints 30 years earlier. An unblinded bronchial challenge test was conducted using increasing concentrations of aqueous extracts of powdered senna leaves. Again, no control substance or control subjects were incorporated into the study protocol. Whole body plethysmography revealed an approximate doubling in specific airway resistance that resolved within 40 minutes of exposure, although dyspnoea attacks were experienced during the night after exposure. Overall, this study does not provide good evidence for senna-induced occupational asthma.

SUPPORTING DATA

In a case study, a worker with suspected occupational asthma was found to have elevated total and specific serum immunoglobulin E (IgE) levels, as measured by radioallergosorbent test (RAST) (Helin and Makinen-Kiljunen 1996). Sera from 5 nonatopic and 11 atopic controls gave negative results, with sera from 2 atopic controls giving slightly positive values. In the same study reactivity was observed following skin prick testing of the subject with senna and a range of common allergens.

In another case study, a subject with suspected occupational asthma was similarly found to have raised total and specific serum IgE levels compared with 10 controls (Baur and Luderschmidt 1983). In the same study, the subject proved positive in a skin prick test with aqueous extracts of powdered senna leaves.

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D13: STAINLESS STEEL WELDING FUME

SUMMARY AND CONCLUSION

Stainless steel welding fume has been implicated in inducing occupational asthma, and is of particular concern since stainless steel contains both chromium and nickel. However, the number of reported cases is small, and evidence from bronchial challenges is conflicting. In addition, several epidemiological studies have shown that welders of stainless steel, as a whole, do not have an increased level of occupational asthma, but that they do have symptoms of irritation found amongst all types of welders.

There is not sufficient evidence to conclude that stainless steel welding fume meets the revised EU criteria (1996) for classification as a respiratory sensitiser (a cause of asthma) and labelling with R42.

INTRODUCTION

Fume arising from the welding of stainless steel has a complex composition which will vary with the welding process (e.g. manual metal arc (MMA), metal inert gas (MIG), tungsten inert gas (TIG)), and the composition of the stainless steel in the parent metal. The health effects of exposure to stainless steel welding fume have been of particular interest because constituents of the fume include nickel and hexavalent chromium, for both of which there is good evidence for induction of asthma (see Compendium entries C34 and C6 respectively). The chromium in MMA stainless steel is primarily in the soluble hexavalent form, while that from MIG/stainless steel is mostly insoluble trivalent chromium (Cross *et al*., 1999). The picture is further complicated because welders are rarely employed at a single type of welding, and over their working life use different welding processes on various metals.

EVIDENCE FOR WORK-RELATED ASTHMA

Five patients with asthmatic symptoms associated with welding gave positive bronchial challenge reactions with stainless steel welding fume, while two welders who had other respiratory disease failed to react (Keskinen *et al*, 1980). Details were reported for only 2 of the 5 patients. Both had been exposed to both mild and stainless steel welding fume at work, and showed a latency period before developing symptoms; case 1 also had occupational eczema associated with hexavalent chromium. At well-conducted bronchial challenge, positive reactions were found on two separate occasions to MMA stainless steel in both cases (late reaction in case 1, immediate in case 2), but not to MMA mild steel; however, both cases also failed to react to MIG stainless steel. The difference in bioavailability of chromium between these two types of stainless steel welding fume may explain the different reactions.

Two welders had several years experience of welding “iron” before developing occupational asthma after stainless steel welding had been introduced (Cirla *et al*., 1982). Both men typically had delayed responses, 4 to 5 hours after exposure in the workplace, and one showed moderate reversible airway obstruction 4 months after the last exposure. Bronchial challenge tests were carried out with fumes from “normal” welding and stainless steel arc welding, though whether in an open or blinded manner was not stated. Both men reacted with clear, positive, delayed responses to the stainless steel welding fume but failed to react to “normal” welding fume.

Six welders with “respiratory symptoms”, 3 of whom had a history of metal fume fever, were investigated by well-conducted bronchial challenge to welding fume from MMA mild steel, and either MMA stainless steel or MMA galvanised steel, according to which provoked symptoms at work (Contreras and Chan-Yeung, 1997). Five of the 6 showed non-specific hyperresponsiveness to methacholine. However, only one of the 4 welders challenged with MMA stainless steel responded positively, and he also responded to MMA mild steel (both immediate reactions). The other 3 failed to respond to either challenge. A similar pattern of positive immediate bronchial

reactions was seen in the other two welders challenged with MMA mild steel and MMA galvanised steel. These findings suggest that a non-specific reaction, perhaps irritant in nature, was occurring to welding fumes in general in these workers.

There have been several studies of groups of workers, which are described below, in which lung function tests have been carried out as part of the investigation, but for which the results have not been presented for individuals but only as group means, with standard deviations. These grouped findings could mask decreased lung function in a minority of welders, especially if others had particularly good lung function.

A comparative study investigated both active welders (i.e. currently working) and those who had left work over the previous 10 years, in order not to miss work-related illness that had led to job loss (Wang *et al*., 1994). For the cohorts, the workers had to have been welding for at least 6 months in the last 10 years, with more than 50% of the total welding time devoted to either stainless steel (MMA) or mild steel (MIG). There were 26 active and 16 former stainless steel welders, with 37 active and 48 former mild steel welders, who were compared with a control group of 30 vehicle assemblers in the same company. Ex-workers had ceased welding approximately 2-3 years before the study took place. All participants were assessed medically, and the majority of current workers also underwent lung function tests. There were no significant differences between stainless steel and mild steel welders (whether previous or active), or between stainless steel welders and controls, in lung function or bronchial hyperresponsiveness to methacholine. There were no clear differences in symptoms, although stainless steel welders had more dyspnoea than controls, and mild steel welders showed increases in cough, phlegm and dyspnoea compared to controls. The authors looked especially for cases of asthma: within the group of 42 stainless steel welders, 2 had symptoms typical of occupational asthma, one in response to stainless steel welding fume and the other to painted steel but not stainless steel. A third had possible welding-related asthma. Of the 85 mild steel welders, 2 had left work due to occupational asthma, while three others had asthma from childhood, or which was apparently not work-related. One of the vehicle assemblers had also had asthma since childhood. This study indicates a similar prevalence (2%) of occupational asthma to stainless steel welding fume as that found in mild steel welders (to unspecified components) compared to 0% in controls, but without specific bronchial challenges or even peak flow measurements across a working week, the accuracy of these figures is open to question.

Ninety welders who had all recently undertaken stainless steel welding in the same fabrication plant underwent spirometry and answered work exposure and symptom questionnaires (Kilburn *et al*., 1990). Thirty-one volunteered to take part in a Monday cross-shift investigation of lung function and exposure patterns. According to what they did during that shift, they were assigned retrospectively to stainless steel welders (mostly TIG, 7 welders), mild steel welders (14) or fitters and helpers (10). The welders, whether smokers or not, had increased prevalence of chronic bronchitis, but no clinically significant reduction of lung function, compared to a referrent random population of men. There were also no changes in pulmonary function across the shift, whether the workers were welding stainless steel or mild steel, or were fitters and helpers.

In a modern cross-sectional study, 134 welders who had been welding for more than 5 years and currently spent more than half their time welding stainless steel were compared with 252 controls from the same factory who were free from respiratory “pollution” (Sobaszek *et al*., 1998). They were examined by medical questionnaire and spirometry; age, height and smoking history were comparable. Respiratory symptoms were more common amongst the welders, especially for morning and/or night-time cough, morning sputum production, dyspnoea and chest tightness, even after adjusting for smoking, but lung function values did not differ between the 2 groups, nor were any cases of occupational asthma reported.

A cross-sectional study was carried out on 3 groups of welders who had worked “mainly” with aluminium (64 welders), stainless steel (46) or railway track (148), with 180 non-welding industrial and railway workers as controls (Sjogren and Ulfvarson, 1985). All the groups of welders had significantly more respiratory symptoms (cough, phlegm, “irritation”) compared to controls, but no

difference in pulmonary function was detected, nor did pulmonary function diminish in subjects with long exposure. Although there was an apparent association between the prevalence of respiratory symptoms and the degree of exposure to ozone (aluminium welders) and chromium (stainless steel and railway welders, the latter using electrodes containing chromium), no other components of the welding fumes were investigated, and the cause of the respiratory irritation was not clearly identified. The study did not reveal any asthma.

A similarly designed study in a factory producing industrial vehicles identified 346 arc welders, of whom 283 welded primarily mild steel, 13 mainly stainless steel and 42 mainly aluminium (Mur *et al*., 1985). A control group was formed of 214 maintenance workers, electricians, etc, who had similar smoking habits to the welders. The study failed to find any significant difference between the groups of welders, or with controls, although welders as a whole tended to have small increases in bronchial responsiveness to acetylcholine, and stainless steel welders tended towards more chronic bronchitis. Again, no cases of asthma were identified in this study.

A poorly-reported but apparently well-conducted study compared respiratory function in 83 stainless steel and 29 mild steel welders from a shipyard (Kalliomaki *et al*., 1982). No difference was observed in the prevalence of cough, phlegm or dyspnoea between stainless steel (TIG and MMA) and mild steel (MMA) welders, although the former had more chronic rhinitis, and occasional reversible attacks of dyspnoea which the authors did not consider to be asthmatic. In general, the mild steel welders had poorer lung function than those welding stainless steel.

Two workers from a group of 25 who welded largely aluminium, but also some stainless steel, reported symptoms of work-related asthma, while none was found in a control group of 25 warehousemen (Nielsen *et al*., 1993). Bronchial responsiveness, conjunctivitis and nasal symptoms were also increased in the welders, although lung function did not differ between the 2 groups.

SUPPORTING DATA

There is no useful information.

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D14: TEA DUST

SUMMARY AND CONCLUSION

The body of evidence for the induction of asthma by tea dust is small in relation to the extent of occupational exposure to the material.. There are relatively few cases of asthma reported in tea-workers, and the small number of bronchial challenge tests that are available have generally not been conducted using stringent protocols. There is, however, some evidence that tea dust can cause effects such as cough and running nose that are irritant in nature.

There is not sufficient evidence to conclude that tea dust meets the revised EU criteria (1996) for classification as a respiratory sensitiser (a cause of asthma) and labelling with R42.

INTRODUCTION

Tea from the tea plant *Camellia sinensis* is produced in a variety of forms: unfermented (green tea), semifermented (oolong tea) and fermented (black tea). It is often further blended to suit particular tastes (Shirai *et al*., 1994). Although there may be some quantitative chemical differences between the various forms of tea, for the purposes of this evaluation all teas produced from *C. sinensis* are considered to be effectively the same material. This evaluation does not consider effects caused by occupational exposure to 'herbal' teas, which are produced from any of a large number of different plant species.

Tea production is a large-scale industry employing many hundreds of thousands of people (de Alwis, 1989). During the refining and packing of tea a dust is formed which is comprised of 'tea fluff', broken tea leaves, particles of inorganic material and traces of silica. The fluff (which is a very fine powder) is hygroscopic and its inhalation has been stated to cause dryness of the upper respiratory tract, chronic rhinitis and pharyngitis (Hill and Waldron, 1996).

EVIDENCE FOR WORK-RELATED ASTHMA

A study was conducted in which a man and a woman who had worked in green tea factories and developed asthmatic and nasal symptoms were exposed by inhalation to a mist of powdered green tea extract or saline (Shirai *et al*., 1994). Another female who had worked in the green tea factory and who from previous work was expected to show a very strong response was exposed to green tea by ingestion rather than inhalation. The 2 individuals exposed to the green tea extract by inhalation showed an immediate fall in force expiratory volume in one second (FEV_1) of at least 30%, while the subject who was given the oral challenge showed a fall in FEV_1 of 37% by 30 minutes after challenge. Changes in FEV_1 following exposure to the saline control were less than 5% in all subjects. Five nonatopic nonasthmatics and 5 asthmatic subjects with no previous green tea dust exposure were also challenged with saline or green tea extract, and did not show any marked change in FEV_1 in response to either challenge. The 3 workers giving asthmatic reactions to green tea also showed immediate bronchial responses to epigallocatechin gallate, the major soluble component of green tea leaves, with falls in FEV_1 of at least 40%. One of these subjects showed such a severe response that subsequent spirometric analysis could not be completed.

Three female tea packers who had reported symptoms such as wheezing, chest tightness, cough and rhinorrhea were given bronchial challenge tests to tea dust, with wood dust serving as a control (Cartier and Malo, 1990). In response to the tea dust, one woman showed a decrease in FEV_1 of 29%, with wood dust having no significant effect, and another of 40%, with a fall of 12% being found for wood dust. The test was negative in the third individual. Peak expiratory flow rate (PEFR) was recorded every 2 waking hours for all 3 women over a number of weeks, and in 2 of them showed a greater fluctuation during the working week than at weekends and holidays. Increases in bronchial hyperresponsiveness to histamine challenge were recorded in all individuals following occupational exposure to tea dust. Tea dust exposure failed to induce any

changes in FEV_1 or bronchial hyperresponsiveness to histamine challenge in an asthmatic control.

A woman who had worked on a tea packing production line for 10 years in an atmosphere described as 'laden with dust', developed symptoms of increased cough and sputum, nasal discharge, sore throat, chest tightness, weakness and lethargy coinciding with a change in source of the tea (Roberts and Thomson, 1988). The symptoms improved during holidays but persisted over weekends. A bronchial challenge was performed in which the patient transferred tea dust between containers for one hour, and 5 hours after exposure the patient showed a 20% decrease in peak expiratory flow rate. On a control day the test was repeated, but 'without exposure to tea dust', when a 5% fall in PEFR was obtained. Over a few weeks PEFR was recorded 4 times a day: there was no clear trend during the normal 5-day working week, but PEFR increased over a 9-day holiday period, and then deteriorated again when work was recommenced. This fall also coincided with a return of the individuals symptoms.

A woman exposed to tea dust whilst cleaning tea bag machines reported intermittent wheezing and shortness of breath which improved at weekends and disappeared during holidays (Lewis and Morgan, 1989). When she was challenged with dextrose and then by tea dust, the control substance produced no response, but with the tea dust there was a fall in FEV_1 of 18% 3 hours after challenge. Prior to the study, the subject had been off work for months without exposure, and an initial challenge with histamine gave a negative response. When challenged with histamine the day after tea exposure she showed a marked increase in bronchial responsiveness.

A case report describes a tea merchant who had suffered from perennial rhinitis for 30 years, and had also had difficulty breathing for 18 years whenever he had inhaled tea dust formed during the preparation of blended tea (Senff *et al*., 1989). It is stated that the symptoms were not markedly suppressed even when he wore a tightly-fitting nasal respirator.

A man who worked in a tea factory and reported asthma attacks in response to exposure to tea fluff was given an inhalation challenge, which is only briefly described (Uragoda, 1970). Although no respiratory measurements were taken, it was reported that after 5 minutes he complained of irritation of the throat, followed by blocking of the nose and a watery nasal discharge which rapidly became profuse. His breathing became laboured and a cough developed.

Two hundred and forty nine employees in a tea packaging plant and 171 controls not exposed to tea fluff completed a questionnaire requesting information on respiratory symptoms (Hill and Waldron, 1996). A statistically significantly larger proportion of tea workers reported chest tightness, blocked or running nose and bouts of coughing with an increased proportion also reporting wheezing and breathlessness. Excluding people with hay fever and smokers, all these symptoms were still greater in tea workers than controls, but differences were only statistically significant for blocked or running nose. The findings of further work involving PEFR measurements taken on work and non-work days are suggestive of a difference between the groups, but this just failed to be statistically significant. Overall, the study authors considered that the symptoms such as running nose and cough reported in the tea workers may be a real occupational effect, but that they represent irritant rather than asthmatic effects of the tea fluff.

The prevalence of respiratory symptoms in 53 workers from a tea-packing plant was examined in a cross-sectional survey in which age, sex, socio-economic status and ethnic group were matched for a control group of field workers from tea estates (Jayawardana and Udupiphille, 1987). Prevalence of chronic respiratory symptoms was obtained by questionnaire, and respiratory measurements were taken. The tea-exposed group showed an increased prevalence of respiratory symptoms, and the mean FEV_1 was statistically significantly lower than for the control group.

One hundred and twenty five tea-blenders with an average service of 23 years in the tea blending industry were interviewed and submitted to a clinical and radiological examination (Uragoda, 1980). The examination was repeated 8 and 31 months later. The prevalence of chronic

bronchitis and asthma was stated to be more than expected in the general population, and it was suggested that the two conditions are aetiologically related to long-term exposure to tea fluff.

In a study of 2 tea-packing plants involving 157 people, statistically significant decreases in FEV_1 and forced ventilatory capacity were recorded during the work shift (Zuhair *et al*., 1981). Other ventilatory indices monitored did not show any trend.

There is anecdotal evidence that hazards associated with tea dust were apparently first reported in 1779, with sudden bleeding from the nostrils and violent coughing occurring in some people engaged in tea blending. In Sri Lanka, even 80 years ago the symptoms were apparently known as 'tea taster's disease' and 'tea factory cough' and more recently 'tea maker's asthma'. A review states that from experience the planters in Sri Lanka knew that tea factory workers suffering from weakness, cough and loss of weight had to be transferred from the factory to the field to allow the symptoms to slowly disappear (de Alwis, 1989).

Other papers (Zuskin *et al*., 1985; Zuskin *et al*., 1988; Zuskin *et al*., 1996) referenced in reviews of tea induced asthma have reported effects in response to inhalation of tea dust or skin prick tests with tea allergens. However, as these use the term tea to include sage, mentha, dog rose and gruzyan (i.e. fruit/herbal tea exposure), the findings of these papers are not considered relevant to exposure to tea from C. sinensis. One other paper (Zuskin *et al*., 1984) has some information on Indian tea, but again is not relevant to this review as the primary exposure for the workers was to herbal teas.

SUPPORTING DATA

Specific immunoglobulin E (IgE) to tea dust has been found in one study (Senff *et al*., 1989) and in addition epigallocatechin gallate, the major soluble component of green tea leaves, has been shown to increase histamine release from the blood of workers with suspected green tea induced asthma (Shirai *et al*., 1997; Shirai *et al*., 1998).

Skin tests have produced variable results, with some studies finding positive results to tea fluff (Uragoda, 1970; Senff *et al*., 1989; Shirai *et al*., 1994) and others not (Roberts and Thomson, 1988; Cartier and Malo, 1990). Positive skin reactions have been observed in response to epigallocatechin gallate (Shirai *et al*., 1994; Shirai *et al*., 1997; Shirai *et al*., 1998).

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D15: TOBACCO LEAF

SUMMARY AND CONCLUSION

The body of evidence relating to the ability of tobacco leaf to induce asthma is small in relation to the extent of occupational exposure to the material. Although a number of studies have suggested that tobacco leaf may cause allergic-type responses, such as rhinitis and wheezing, and reduced respiratory function in some exposed individuals, there is little evidence for induction of asthma itself, with only one case including a positive bronchial challenge response. Tobacco leaf has been shown to contain numerous high molecular weight proteins which have been shown to stimulate the formation of specific immunoglobulin E (IgE) in animals and humans, and positive skin prick tests with tobacco leaf extract also suggest that an immunological mechanism may be involved in any allergic responses. Raw tobacco leaf is often contaminated with moulds and fungi, and several reports demonstrate that these agents may also produce an allergic response.

There is not sufficient evidence to conclude that tobacco leaf meets the revised EU criteria (1996) for classification as a respiratory sensitiser (a cause of asthma) and labelling with R42.

INTRODUCTION

Tobacco leaf is harvested and processed for the production of cigarettes and cigars, and the industry employs many thousands of workers in many countries throughout the world. Being a natural product, raw tobacco leaf undoubtedly contains many potentially immunologically- active high molecular weight proteins. In addition, tobacco processing requires a humidified environment which encourages the growth of microorganisms such as mould and fungi, many of which are known to cause symptoms of irritation and allergic conditions (Husman, 1996).

Although there are several types of tobacco plant to which workers may be exposed occupationally, few studies have characterised the identity of tobacco encountered in their study population. In volunteers skin tested with several types of tobacco extracts (Burley, Virginia and Turkish), the overall pattern of skin reactions was comparable for each type, although some subjects were reported to only be sensitive to some of the extracts (Fontana *et al*., 1959). This suggests that there may be differences in the immunological potential of different types of tobacco. However, due to the limited characterisation of tobacco exposure in the available studies, this assessment regards tobacco as a generic material and does not attempt to distinguish between different types. Reference in studies to green tobacco leaf, or just tobacco leaf, has been interpreted as referring to raw, unprocessed tobacco leaf, rather than a specific type of tobacco.

EVIDENCE FOR WORK-RELATED ASTHMA

After 4 years employment at a tobacco factory, a female subject started to experience rhinitis and asthma when exposed to tobacco (Gleich *et al*., 1980). In a poorly described bronchial challenge test, raw tobacco leaf extract (TLE) caused reductions in a number of lung function parameters, including a 49% decrease in forced expiratory volume in one second (FEV_1). A comparable response was observed following challenge with tobacco extract free from mould and fungi, suggesting that the effect was due to tobacco leaf itself and not to contaminating agents. The asthmatic symptoms resolved within 4 hours and were not followed by any late reactions. Control subjects gave a negative response to TLE, while a similar challenge with cured leaf extract caused a less pronounced reaction. In addition, the subject was given a nasal challenge with TLE that caused a four-fold increase in nasal resistance and a typical attack of rhinitis.

A number of studies have demonstrated reduced lung function in tobacco workers. Amongst 16 workers exposed to tobacco dust in a Danish factory, there was a higher prevalence of symptoms consistent with asthma than in a reference population, with mean forced vital capacity (FVC) and

FEV_1 both statistically significantly lower (Lander and Gravesen, 1988). The mean diurnal change in peak expiratory flow rate (measured 4 times a day over a 7-day period) was statistically significantly increased (by 52%) compared to control; for half of the subjects this change was greater than 20% on one or more days.

Among 528 female Yugoslavian tobacco workers exposed to tobacco dust, there was a significant decrease in mean FEV_1 and FVC during a work shift (Valic *et al*., 1976). This population also had an increased prevalance of chest tightness (11 v 3%) and wheezing (10 v 1%) compared to controls.

Mukhtar *et al* (1991) demonstrated statistically significantly decreased ventilatory capacities (FEV_1 and FVC decreased by 15 and 13% respectively) and reduced expiratory flow in 195 Libyan subjects occupationally exposed to tobacco dust. In contrast, a study of 106 Finnish tobacco workers found no difference in FVC or FEV_1 between workers and referents (Uitti *et al*., 1998).

In another study, 349 male and 454 female Italian tobacco workers displayed an increased prevalence of asthma and wheezing (up to 12 and 41% respectively) compared to referents (Viegi *et al*., 1986).

Among 75 workers at a Danish tobacco factory, there was an increased prevalence of cough and shortness of breath on exercise (Kjaergaard *et al*., 1989). There were reductions in FEV_1 and FVC in tobacco workers but after adjustment for smoking habit, these changes were only apparent in light smokers. There was no change in FVC and FEV_1 over a shift period. A larger proportion of tobacco workers (17 v 6%) exhibited nonspecific bronchial hyperresponsiveness on challenge with histamine.

In a group of 101 Romanian tobacco workers, 8% had allergic-type clinical conditions (dermatitis, rhinitis, asthma), and 4 out of 23 tested displayed asthmatic symptoms in response to tobacco (Popescu *et al*., 1964). Smoking increased the incidence of allergic responses to tobacco. Poorly reported bronchial challenge tests with TLE did not cause any ‘clear-cut’ responses.

There is some limited evidence that the fungi and moulds present on raw tobacco leaf may be involved in inducing asthma. A female tobacco worker experiencing asthmatic symptoms during shifts was found to produce a late asthmatic reaction following bronchial challenge with one of a range of fungi commonly found on the tobacco, and to have specific IgG antibodies to those fungi (Lander *et al*., 1988).

SUPPORTING DATA

Analysis of TLE has indicated that it contains up to 20 high molecular weight (17- 68 kdalton) proteins, with cured tobacco leaf extract containing fewer proteins, probably due to denaturation during the curing process (Chu *et al*., 1970; Becker *et al*., 1976; Gleich and Welsh, 1979). Rabbits and guinea pigs, immunized with TLE or cigarette smoke condensate, produced up to 10 specific IgE antibodies (Chu *et al*., 1970; Lehrer *et al*., 1978; Gleich and Welsh, 1979). Similarly, rabbits developed specific antibodies following repeated subcutaneous injection of tobacco extract (Zussman, 1968). Specific IgE antibodies to TLE have also been observed in humans (McDougall and Gleich, 1976; Gleich *et al*., 1980). Passive transfer tests from individuals who experienced symptoms consistent with asthma on exposure to tobacco smoke conferred tobacco sensitivity in the recipient subjects (Rosen and Levy, 1950; Zusman, 1968).

Several studies have demonstrated skin reactions to TLE in workers who exhibit asthma-type symptoms in response to tobacco leaf. A female tobacco worker who experienced rhinitis and asthma in response to tobacco gave a positive skin scratch test with TLE (Gleich *et al*., 1980). Serum IgE binding, as measured by the radioallergosorbent test (RAST), demonstrated 15.4 and 5.5% binding to TLE and cured tobacco leaf extract respectively. In contrast, among 15 subjects who exhibited ‘allergic-type’ reactions to tobacco smoke, IgE binding was only slightly higher in

the 7 subjects giving positive skin reactions than in the 8 giving negative reactions (1.9 v 0.9% respectively; McDougall and Gleich, 1976). The extent of binding was not reduced by pre-incubation of the sera with antigen, suggesting that the binding was non-specific.

An ex-tobacco worker who had been relieved from duty because of 'allergic' reaction to tobacco dust gave a positive skin prick test to several tobacco extracts (Uitti *et al*., 1998). In other studies a proportion of symptomatic workers gave positive skin tests to TLE (Popescu *et al*., 1964; McDougall and Gleich, 1976; Viegi *et al*., 1986; Kjaergaard *et al*., 1989). Tobacco workers with no adverse response to tobacco gave negative skin prick tests to TLE from various species of tobacco plant, even though titres of antibodies to tobacco were higher in workers compared to referents (Uitti *et al*., 1998).

Extrinsic allergic alveolitis has been reported in workers growing or processing tobacco, with the suggestion that it may be due to exposure to tobacco and/or moulds present on the tobacco leaves (Huuskonen *et al*., 1984; Huuskonen *et al*., 1986; Chomenko *et al*., 1990; Uitti *et al*., 1998).

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SECTION E: Substances on the ACTS/WATCH programme on account of concerns over respiratory senstisation

Alpha amylase

p-Phenylenediamine

Piperazine

Subtlisins