GUIDANCE FOR THE MEDICAL SURVEILLANCE OF WORKERS EXPOSED TO COMPLEX SALTS OF PLATINUM

INTERNATIONAL PLATINUM ASSOCIATION

PREFACE

Allergy to complex halogeno salts of platinum remains a significant occupational health hazard wherever halogenated platinum salts are handled. While the incidence of this condition has declined over the last 25 years through improved engineering and safer work practices, it nonetheless continues to pose a significant medical challenge, as well as a financial and legal problem for employees and management.

Many studies have been made of the allergy and review of these has shown a diversity of terminology and standards which has made it difficult to compare results. In order to encourage a uniform approach and common standards for tests, the Medical Committee of the International Platinum Association has prepared this review of medical surveillance techniques and diagnostic standards.

Guidance and justification is given on the components of a medical surveillance programme and the frequency of such tests.

The guidelines provided in this document are intended to alert the user of chloroplatinate salts to the risk of the health hazards associated with exposure to them. Any medical surveillance programme specific to a particular facility should be developed in consultation with appropriate medical and occupational health professionals and may vary from the general outline provided here. Factors which should be considered in developing a programme appropriate to a facility include the degree and frequency of exposure, as well as the past history of allergy in that facility or similar operations.

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This work has been commissioned by the International Platinum Association for publication to its members. It has been prepared and is intended to assist them and their health professionals and advisers who may be responsible for initiating or advising on medical surveillance of workers exposed to complex halogeno salts of platinum. It is not intended for any other purpose.

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1.0 INTRODUCTION

Symptoms in workers handling halogenated platinum salts were first reported in 1911.[1] Cross sectional surveys of the health of platinum refinery workers and in platinum bearing catalyst production in past years have shown allergic symptoms affecting the respiratory tract and skin to be common.[2,3,4,5,6,7]

The symptoms are generally those of a Type I allergic reaction and the results of skin prick testing (SPT) with complex salts of platinum were shown to correlate well with symptoms which were provoked by direct inhalational challenge using the same salts.[8] Occasional cases have presented with chronic dermatitis and a positive patch test reaction. However in contrast to contact urticaria, contact dermatitis (allergy) to platinum salts has not been convincingly demonstrated.

Using the technique of SPT it has been demonstrated that it is the complex halogeno platinum salts which are allergenic. The potency is proportional to the number of leaving halogen ions.[9] Exposure to complex platinum compounds in which the halogen ion is not complexed to the platinum ion have not been associated with sensitisation[10].

Major reviews of the health and environmental effects of platinum compounds have been published by the US National Academy of Science[11] and by the International Programme on Chemical Safety of WHO.[12] Guidance on medical surveillance has previously been published.[13,14]

Techniques which have been introduced for the investigation of occupational allergy include the Radio Allergo Sorbent Test (RAST) for specific Immunoglobulin E (IgE) to platinum salts.[15,16] Specific bronchial challenge with chloroplatinate salts has been used for diagnosis[8,17] and tests for measurement of non-specific bronchial hyperresponsiveness have been used in follow up studies.[18,19,20,21] For most occupational physicians who are responsible for medical surveillance, these tests remain research tools available only in specialist units and for some of them the full value may not yet have been proven. In the review that follows, the place of the various routines and tests are discussed to provide the basis for a practical and effective medical surveillance programme.

Refining and use of platinum and platinum group metals may involve exposure to many other hazardous chemicals - acids, alkalis and organic compounds. The risks from exposure to these must be considered alongside those due to platinum salts. Account must be taken of these in a medical surveillance programme, the purpose of which is to prevent the aggravation of pre-existing conditions and by early recognition of the allergy prevent the development of persistent adverse effects.

2.0 DEFINITION AND CHARACTERISTICS OF THE ALLERGY

Allergy to Complex Halogenated Salts of Platinum (ACHSoP) is an acquired hypersensitivity to the complex salts of platinum which becomes manifest after a variable period of symptomless exposure. The clinical characteristics include one or more symptoms and signs of dermal, ocular and nasal allergy and/or asthma.

"Hypersensitivity" is an umbrella term described as causing objectively reproducible symptoms or signs, initiated by exposure to a defined stimulus at a dose tolerated by normal subjects. “Allergy” is a hypersensitivity reaction initiated by immunologic mechanisms and describes the expression of the hypersensitive status in terms of clinical symptoms and signs. The term “sensitization” in this context applies to the state in which an immunologic change can be demonstrated by a positive skin prick test but at which stage there are no symptoms or signs.

Tests for sensitization are directed to detection and measurement of specific antibodies - in particular to specific IgE. Skin prick test (SPT) using chlorplatinate salts is the best, most reproducible and objective test to demonstrate the presence of specific IgE.

The signs and symptoms of the allergic response are similar to those provoked by other inhalable or dermal allergens and are not specific to platinum salts. The symptoms include.[1,2,3,11,12,18,22]

* Conjunctivitis with itching and lacrimation.

* Rhinitis with nasal obstruction, rhinorrhoea, sneezing attacks (3 or more consecutive sneezes).

* Bronchial effects include cough, tightness of the chest, shortness of breath and wheeze. Related chest symptoms may be expressed as a weight on the chest or constriction of the throat.

These symptoms usually occur in the allergic subject within a few minutes of exposure but in some cases the asthmatic response may be delayed and cause nocturnal symptoms.

* Urticaria may occur on direct contact with platinum salts.

* Other dermal symptoms may include erythema of exposed surfaces and pruritus.

* Contact dermatitis may occur but is not common.

3.0 MECHANISM OF THE ALLERGIC RESPONSE

The allergic symptoms indicate a Type I reaction mediated by IgE.[8,9,22] Complex salts of platinum probably act as a hapten and by combination with a protein, form an antigen which then stimulates the production of IgE. Human serum albumen (HSA) has been studied as the most likely protein to act as a ligand.[23]

Specific IgE to Pt-HSA is produced and attaches to the mast cells which are close to epithelial surfaces.[24] Subsequently challenge by more antigen (from inhalation of chloroplatinates and binding to HSA) causes a cross linking of the specific IgE antibody which results in release of mediators such as histamine and phospholipase into the tissues. These cause vasodilation and oedema, bronchial smooth muscle contraction and mucus secretion.

Other cell types including T cell lymphocytes, dendritic cells and eosinophils, together with the cytokines released by them, are important factors in mediating the allergic response and regulation of IgE.[25,26]

4.0 RISK FACTORS IN CAUSATION OF THE ALLERGY

ACHSoP is specific and only occurs following exposure to the complex halogenated platinum salts. With good control systems these salts do not occur outside the workplace and thus the allergy is occupational in origin. Prevention and control are dependant on technical and environmental systems and good personal work hygiene practices. The use of other platinum compounds in which the platinum is not complexed to a halide is not associated with the allergic response.[10]

Factors which increase the risk are smoking [10,27,28,29,30] and exposure dose.[28,30] Where a high incidence of ACHSoP has been reported, the relative risk due to smoking is between 4 and 8.

Atopy is a personal or familial tendency to produce IgE antibodies in response to exposure to low doses of allergens and to develop typical symptoms such as asthma, rhinoconjunctivitis, or eczema/dermatitis. The relative risk due to atopy in one study was 2.29 but was not statistically significant (CI 0.88 to 5.99).[27]

The significance of human leucocyte associated antigen (HLA) has been studied in cases and matched referents. HLA-DR3 phenotype was more common in cases than referents with odds ratio of 2.3 but this association was much stronger in cases who had lower levels of exposure (OR infinite) whereas H6A-DRG was less common among the cases than referents and again the association was stronger in the group with the lower exposure levels.[31]

When risk factors are to be considered with respect to pre-employment entry criteria, the risk conferred by that factor needs to be related to the quantified risk for subjects without that factor in that particular workplace. Ways of calculating incidence and risk are considered in Appendix 9.3.

5.0 **TREATMENT**

Treatment of the symptoms of ACHSoP is the same as for other allergies and asthma. The objective should be to prevent further exposure to the allergen and stimulation of specific IgE production.

One case has been reported of treatment by specific hypo-sensitisation.[32] Though successful, the subject developed serum sickness during the treatment. The effectiveness of the treatment declined when exposure was temporarily discontinued so that desensitisation had to be repeated. The major risks due to desensitisation make it a treatment that cannot be recommended.

6.0 PROGNOSIS

As asthma is a disease characterised by reversible airways obstruction, it might be expected that cessation of exposure to the specific allergen would lead to complete recovery. However this has not been the experience with occupational asthma due to other sensitising agents, particularly when exposure has continued after asthma has developed.[33,34]

Several follow up studies have been made of ACHSoP to look at the persistence of asthma. In one study in which medical surveillance was performed every 3 months when cases had ceased exposure immediately upon diagnosis there was no increased incidence of bronchial hyperresponsiveness in cases when compared with matched controls at examination 12 to 24 months later.[19] This was accompanied by reversal of SPT reaction though symptoms of breathlessness were more common in cases than controls. In another study cases subject to surveillance at 12 month intervals and who ceased exposure on diagnosis were followed up 19 (range 6 - 30) months later and showed a reversal of skin test reactivity, decline of symptoms and decrease of bronchial responsiveness.[21]

Decline in sensitivity and symptoms was also shown following transfer of cases to work with lower exposure.[35] However other studies have shown that when exposure was allowed to continue after symptoms had occurred, bronchial hyperresponsiveness persisted in some subjects.[18,20]

In order to prevent episodes of asthma and development of non specific bronchial hyperresponsiveness, exposure should cease as soon as possible after the diagnosis has been confirmed.

An increase in total IgE was noted in both sensitized and unsensitized subjects during a 24 months prospective study at a platinum refinery.[16] Total IgE levels at outcome of the study had increased in more sensitized subjects and median levels were higher than in unsensitized subjects. The likelihood of an increase in total IgE was nine times greater in subjects sensitized to platinum salts, and five times greater with higher platinum salt exposure. The study was not continued once exposure had ceased.

7.0 METHODS AND STANDARDS FOR INVESTIGATION AND DIAGNOSIS

ACHSoP is a clinical condition in which characteristic symptoms occur. The diagnosis is confirmed by assessment of their relation to work supported by tests of the immunological response with objective measurements of respiratory effects.

The methods for investigation and diagnosis of ACHSoP may be considered in 3 subheadings:

* Symptomatology
* Immunology
* Respiratory function

Biological monitoring has been performed as a research tool.[30,36] An association has been shown between levels of exposure and platinum levels in urine. In a 5 year cohort study the serum platinum levels were not predictive of sensitization as demonstrated by a positive skin prick test. [37]

7.1 Symptomatology

Questionnaires for respiratory symptoms have been widely used for cross-sectional studies. Standardised questionnaires have been validated[38,39] and are useful for initial or cross-sectional surveys, however when direct questions are being asked about specific work related symptoms at regular intervals, the standard questionnaires have been found too lengthy and abbreviated forms are required.[40] Positive answers should be explored more fully to assess relationship to work.

Upper respiratory symptoms are common in the general population[41] and direct questioning for these has low specificity. For asthma the questions most predictive are:

"Has your chest felt tight or your breathing become difficult?
Has your chest sounded wheezy or whistling?"

In some occupational settings when it is known that a diagnosis of occupational asthma requires removal from exposure, symptoms may be denied initially by subjects on routine questioning, but later when they are of such severity that the individual acknowledges the need to cease exposure, long standing symptoms may then be admitted. This indicates a need to support the use of questionnaires by studies of immunology and lung function.

7.2 Immunology

Type I allergic reactions are mediated by IgE thus tests for the detection of antibodies have been directed towards measurement of total IgE and specific IgE in serum.[15] Specific IgE in skin can be detected by direct challenge using the skin prick test and measuring the response to serial dilution of platinum salts.

7.2.1 Specific and total IgE

High levels of specific IgE measured by RAST correlate with SPT reaction but SPT may be positive with low levels of specific IgE.[15] There is poor correlation with symptoms.

The RAST for specific IgE is complex and slow. It has not been helpful in establishing a diagnosis when the SPT has remained negative. The test is more appropriate for workforce surveys than as part of the diagnostic investigation for individual subjects.[40] A correlation of specific IgE with total IgE has been found making the interpretation difficult in subjects with high total serum IgE.[16,42]

RAST for specific IgE has usually been performed in research laboratories handling large numbers of study and control samples for comparison. Commercial methods may not match the reproducibility of results when tests are performed on small numbers of samples. When individual tests are performed, control samples should be examined.

Levels of total IgE were studied prospectively using the Phadiatop® method in 78 non-atopic refinery workers[16]. Pre-exposure levels of total IgE were not predictive of subsequent sensitization but during the two year study more sensitized than non-sensitized subjects became Phadiatop® positive with total IgE > 100kU/L.

7.2.2 Skin Prick Test (SPT)

Skin testing methods for investigation of allergies have included intra-cutaneous, scratch and prick tests.[43,44] Intra-cutaneous tests may be hazardous in highly sensitised individuals.[45] Severe reactions to scratch test with platinum salt have occurred. The prick test is the most widely used and recommended test for demonstration of Type I allergy - including assessment of atopic status by response to common inhaled aeroallergens. It is the recommended method for serial observation for the development of sensitivity to platinum salts.

7.2.2.1 **SPT Technique**

Prick tests are performed on the volar aspect of the forearm after cleaning with water. A drop of the test solution is placed on the skin. The tip of a 25G disposable needle is introduced at an acute angle to the skin through the drop into the epidermis and lifted gently. A perceptible "plinck" may be detected. The skin should not bleed.

As an alternative to use of a needle, a sterile lancet may be pressed into the skin at right angles through a drop of the test solution. In all tests a negative control solution should be used for comparison. A positive control using histamine may be used.

The volume of solution introduced into the epidermis by the SPT is 3×10^{-6}ml [46]. The platinum salts to be used - concentration and preparation of the test solution are described below.

The test is read after 10 to 20 minutes - the diameter of the weal is measured and recorded. The size of the flare is not recorded. Weal size can be easily measured using a skin test reaction measure (Bencard®). In the case of irregularly shaped weals, the mean of the greatest diameter and the diameter at right angles to it can be reported.

For the documentation, an impression can be recorded by outlining the weal in ink, applying transparent or translucent adhesive tape over the test site then lifting off the mark and sticking the imprint to the record.

A positive result is one in which the diameter of the weal in response to the test solution is 3mm greater than the diameter of any weal produced by the negative control solution.

A positive response to platinum salt solution requires confirmation by repeat tests at serial dilution.

Occasional late reactions may occur between 8 and 24 hours later. They may relate to symptoms but too few are reported for their significance to have been analysed fully.

7.2.2.2 **Test Solutions**

Factors to be considered in preparation of test solutions are the salt, the diluent and the concentration.

The salt:

Studies of platinum refinery workers showed the strongest correlation between symptoms and SPT using three platinum salts, ammonium hexachlorplatinate $(NH_4)_2PtCl_6$, sodium hexachlorplatinate Na_2PtCl_6 and sodium tetrachlorplatinite Na_2PtCl_4. Chlorplatinic acid H_2PtCl_6, due to its low pH, causes false positive skin reactions if used for SPT.

In the majority of cases of ACHSoP, there are positive responses to all three salts. Due to its high stability there has been agreement to use one salt i.e. Na_2PtCl_6 for routine surveillance and as the standard for subsequent studies. If symptoms strongly suggest ACHSoP and the SPT using Na_2PtCl_6 is negative, then SPT using the other complex salts may be indicated to confirm the diagnosis of ACHSoP.

The diluent:

Initially platinum salt solutions were prepared in glycerol carbol saline (GCS). This has been shown to have a destabilising effect on the platinum salt and requires frequent preparation of test solutions.

Solutions prepared in 0.9% sodium chloride (physiological saline) have been shown to be stable for 6 months depending on storage conditions and provoke comparable SPT reactions in known cases, when tested alongside freshly prepared solutions using GCS.

The recommended test solution is sodium hexachorplatinate in 0.9% sodium chloride.

A reduction in pH of stored test solution has been noted over 4 weeks but this has not had an effect on SPT response. Use of a phosphate buffer solution is recommended, if the solutions are to be used for specific bronchial challenge but are not necessary for skin prick testing. Buffered solution is stable for at least 6 months.

The concentration:

Solutions containing 10^{-3}g/ml have been established as safe and positive results - correlate well with clinical disease.[7] Solutions with 10^{-2}g salt/ml cause non specific histamine release in skin.[9] Mild systemic reactions have been reported in symptomatic cases when solutions containing 10^{-2} mol/litre (4.86×10^{-3}g/ml) were used for SPT.[17]

An initial positive reaction to the platinum salt solution requires confirmation by repeat testing and the degree of sensitivity can be measured by testing with serial dilutions of the test solution down to 10^{-9}g/ml.

It is recommended that the standard solution for screening SPT should use Na_2PtCl_6 at a concentration of 10^{-3}g/ml in 0.9% NaCl solution. Serial ten fold dilution of this made up in 0.9% NaCl will be used to measure the degree of sensitivity. A protocol for preparation of the test solution is given in Appendix 9.4.

7.2.2.3 **Interpretation of the SPT Result**

Interpretation of the SPT to some extent depends on the use made of the result. When the SPT is used for routine screening of asymptomatic subjects, a variable and often non-repeatable reaction has been seen with a weal of 2mm diameter or less. (Diameter is taken as the measure by which the diameter of the weal with the test solution exceeds the diameter of any weal which occurs with the negative control). A positive SPT reaction should be 3mm or more and consistent when repeated for confirmation.

For investigation of a case with definite work related symptoms a change in the SPT reaction using 10^{-3}g/ml from negative to a 2mm diameter weal may be confirmation of ACHSoP if the reaction is consistent and repeatable.

7.2.2.4 **Specificity and Sensitivity**

Positive SPT reactions have been seen only in people who have had previous exposure to platinum salts. It is thus 100% specific for identification of subjects who develop hypersensitivity to platinum salts.

Cases of ACHSoP may present with symptoms yet have a negative SPT. Confirmation of cases by assessment of work relatedness or specific bronchial challenge suggest a sensitivity for the SPT about 80-90%.

When exposure to platinum salts continues at the same level the positive SPT is 100% predictive for development of symptoms. [28]

7.2.2.5 **Comparison between SPT and Work Exposure**

Concerns have been expressed by some people as to whether SPT could induce hypersensitivity to platinum salts. The SPT introduces 3×10^{-6}ml into the epidermis[46] thus the screening test using 10^{-3}g/ml gives a challenge dose of 10^{-9}g. This is considerably lower than the amount of platinum salt that might be inhaled in a normal work shift. Long term surveillance using Na_2PtCl_6 for SPT on unexposed control subjects has not resulted in any cases of sensitisation. [30,47]

7.2.3 **Other Markers of Allergy**

Other investigations of ACHSoP have included measurement of eosinophilia in blood and mucus, also histamine release from basophils. These tests are non specific and do not contribute to the investigation of individual cases nor epidemiological studies. They do not form part of a general surveillance programme.

7.3 **Respiratory Function**

Studies of respiratory function concentrate on measurement of volume and flow by spirometry to demonstrate changes due to work exposures and non specific or specific bronchial challenges.

Measurement of gas transfers are not indicated for routine surveillance or diagnosis of occupational asthma.

7.3.1 **Spirometry**

Though routine spirometry in the clinic has a low sensitivity for detection of occupational asthma in the absence of acute symptoms, it is an essential element in the medical surveillance for platinum salt exposure. It provides objective evidence of variable air flow obstruction when it occurs. This is the cardinal feature of asthma and its relation to work.

7.3.1.1 **Equipment and Methods**

High standards of equipment and performance are required. Comprehensive guidance has been published on standardised lung function testing including reference values.[48,49,50,51] Guidelines have also been prepared for the diagnosis of occupational asthma[52] and evaluation of impairment/disability.[53]

Personnel responsible for spirometry should be trained for this and their continuing competence documented.

The minimum requirement of equipment for assessing ventilatory function is a spirometer which can record vital capacity (VC), forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1). The spirometer should produce hard copy graphs large enough to allow recognition of unacceptable manoeuvres and to make hand measurements.

7.3.1.2 **Spirometry for Acute Symptoms**

Spirometric measurements in acutely symptomatic workers provide objective evidence to corroborate symptoms of asthma, to confirm the presence of airflow obstruction and its severity. Symptoms of airflow obstruction are relatively non-specific and clinical auscultation is less sensitive than spirometry in mild degrees of airflow obstruction. Reliance on reported symptoms and chest auscultation only may therefore be misleading.

Spirometry should be available at any time of the work day, so that measurements can be made whenever a worker experiences or complains of symptoms of cough, wheeze, chest tightness or shortness of breath. Spirometry is often difficult to perform under acute circumstances and requires particular skill on the part of the occupational health staff, but every effort should be made to obtain acceptable and reproducible tracings. Measurements made under these conditions are particularly important for certification and compensation purposes.

Detailed documentation of the work history and activity prior to the onset of symptoms must also be recorded, together with an assessment of the nature and severity of exposure. Exposure to irritating gases (e.g. chlorine) should also be noted.

Response to an inhaled bronchodilator should be measured routinely if there are features of airflow limitation or significant changes from pre-employment values.

7.3.1.3 **Across-Shift Monitoring**

Across-shift monitoring may be useful for documentation of variable airflow obstruction at work in some cases. Usually episodes of airflow obstruction at work are acute and well defined, so that the affected case presents with symptoms. Insidious loss of function over a work day seldom occurs.

7.3.1.4 **Peak Expiratory Flow Rate Monitoring**

The evaluation of peak expiratory flow rate (PEFR) recordings is a widely used method to assess occupational asthma and a good way to establish the relationship to work.

It is generally recommended that PEFR should be measured every 4 hours during waking hours over working periods separated by a period away from work.

Measurements at work should be over at least a 2 week period and the period off work should be at least 1 week. There should be at least 3 blows each time and the variation between blows should be less than 10%. The best of the 3 blows is used for analysis.

PEFR is usually analysed qualitatively by simple visual assessment and occupational asthma is considered present if the PEFR appears to be lower at work, or if it shows more within day variability at work than at weekends or during holidays.[54]

Although various quantitative indices of PEFR variability have been proposed, none have been shown to be any better than visual analysis by experienced physicians. When assessed against a diagnosis of occupational asthma made by specific bronchial provocation testing, the sensitivity of PEF monitoring is 81 to 87% and the specificity 74 to 90%.[55]

Though PEFR monitoring is considered a simple way to evaluate the response of bronchial obstruction to work, in practice, the value is limited in many cases because of poor compliance in the absence of direct supervision. Because peak flow meters are so portable, thus allowing their use in the workplace, monitoring of PEFR in relation to exposure is an approximation of specific bronchial provocation.

7.4 Bronchial Provocation Tests

7.4.1 Non Specific Bronchial Hyperresponsiveness (NSBH)

Subjects with occupational asthma usually exhibit non specific bronchial hyper-responsiveness. This is demonstrated by a reduction of FEV_1 following the inhalation of a non specific stimulus such as histamine, methacholine or cold air. Measurement of NSBH provides confirmation of asthma quickly under controlled conditions.

There is no internationally agreed standard for tests of NSBH. Three methods have been used for study of ACHSoP.

7.4.1.1 Cold Air Challenge

Inhalation of cold dry air has been used in two epidemiological studies of ACHSoP [18,19] and gives consistent results. The equipment is bulky and impracticable for most purposes but the method does reproduce under controlled conditions a situation that is a common provocation of asthma. The method requires a consistent rate of ventilation for a set period (60-65 L/min for 4 min) with cold dry air (inspiratory temperature -40^{o}C

in one study[18], though -15°C to -20°C is more often used[19]). The response of a normal group is used to establish a normal range for change of FEV_1 and NSBH is considered to occur when the drop in FEV_1 exceeds the mean change plus 2 SEM.

7.4.1.2. **Methacholine Inhalation**

Standardised challenge testing with pharmacological stimuli has been the subject of international review.[48] The method derived from Gonsior [56] requires inhalation of methacholine from a jet nebuliser using methacholine solutions of increasing strength. Specific airway conductance (sGaw) is measured one minute later. Increasing doses are used until a 50% reduction of the sGaw has been achieved. The dose which provokes a 50% drop in the sGaw is calculated (PD_{50} sGaw). A PD_{50} sGaw of 1 mg or less of methacholine, indicates NSBH. Measurement of sGaw requires the use of body plethysmography.

In the method derived from Cockroft [57] doubling concentrations of methacholine are inhaled from a Wrights nebuliser calibrated to deliver an output of 0.14ml/min via a loosely fitting face mask. FEV_1 is used as the measure of airway calibre. The inhaled concentration is increased until a drop of FEV_1 of 20 percentage points or more has been achieved, or until the highest concentration of 16mg/ml has been used.

The percentage drop of FEV_1 is plotted on semi log graph paper against the inhaled concentration of methacholine and the concentration which provokes a 20% fall of FEV_1 is calculated. This is the PC_{20}. A value of 8mg or less is indicative of NSBH.

7.4.2 **Specific Bronchial Provocation**

Specific bronchial provocation requires the inhalation of the allergen under controlled conditions which allow for measurement of response. The place of specific bronchial provocation in the diagnosis and investigation of occupational asthma is subject to differences in national attitudes and legal requirements. It is generally agreed that specific bronchial provocation is warranted for the investigation of someone with asthmatic symptoms but a negative SPT in order to confirm the diagnosis. There is no general agreement that specific provocation is justified in subjects who are known to have sensitivity to an allergen as shown by SPT in whom measurements of NSBH may be sufficient to establish a diagnosis of occupational asthma. Guidelines have been published in Europe[52] and America.[58]

As with tests for NSBH, there is no internationally agreed standard for specific provocation and tests may be considered in two groups - simulation of workplace exposures and measurement of dose response relationships.

7.4.2.1. **Workplace Simulation**

In the method developed by Pepys the subject, in an enclosed cabinet, pours dry lactose powder (250g) from one tray to another for 30 minutes[59]. FEV_1 is measured before and immediately after the test and every ten minutes for the first hour then hourly through the rest of the day. NSBH using methacholine is determined before testing and each subsequent morning.

$(NH_4)_2PtCl_6$ is added to the lactose from day 2 onwards in increasing doses of 1 mg, 2 mg, 5 mg and 10 mg on consecutive days.

This method has been shown to achieve measured levels of platinum in air of 2µg/m^3 at the highest dose.

A result is considered to be positive when there is a drop of FEV_1 of 20% following the challenge or NSBH is induced with a reduction of the PC_{20} to 8 mg or less.

7.4.2.2. **Aerosol Generation**

Whole body plethysmography has been used to measure the response of sGaw to inhaled allergens[56] to determine PD_{50} sGaw. Na_2PtCl_6 in 0.9% phosphate buffered saline (PBS) may be used at serial dilution for inhalational challenge to establish a dose response curve from which the PD_{50} sGaw may be calculated. In the technique reported[20] hexachloroplatinic acid was used, buffered with NaOH and diluted with saline.

The starting dose (10 breaths) is determined from the SPT response and is usually between 10^{-7} and 10^{-5} mol/l with concentration of the challenge solution increasing 10 fold every 15 minutes, until there is a fall of 50% of sGaw or the maximum concentration of 10^{-2} mol/l has been used. sGaw is measured regularly during the subsequent 60 minutes and then PEFR for the next 6 hours. A reduction of sGaw of 50% using a concentration of 10^{-2} mol/l or less is considered a positive result. This is equivalent to the exposure limit for soluble platinum salts.

Determination of PC_{20} for FEV_1 to inhaled allergen requires a simpler set up[60]. PC_{20} methacholine is determined - then a solution of Na_2PtCl_6 in PBS is delivered through a

Wright nebuliser for 2 minutes (calibrated to deliver 0.14ml/min). A Hans Rudolf valve fitted with a low resistance absorption filter is attached to the expiratory port to prevent dispersion of the allergen to the atmosphere. The starting dose for inhalation is determined from the lowest serial dilution giving at least a 2mm weal reaction on SPT (usually between 10^{-7} and 10^{-5} g/ml). FEV_1 is measured at 5,10 and 15 minutes after the inhalation. If the drop in FEV_1 is less than 20%, the next stronger solution is used until a drop of 20% is achieved, or the maximum concentration of 10^{-3} g/ml has been used.

A positive test is defined as a fall in FEV_1 of 20% or more with a platinum salt concentration equal to or less than 10^{-3}g/ml. PEFR is monitored with a Mini-Wright peak flow meter for 24 hours after the test. A late asthmatic response (LAR) defined as a greater than 20% fall in PEFR, with or without asthma symptoms (cough and/or tight/wheezy chest), is also considered a positive result.

The choice of technique will depend on the purpose of the test i.e. for diagnosis or compensation, the local or national requirements for evaluation of disability for compensation and on the facilities and expertise available.

Specific bronchial challenge requires the presence of an experienced physician and appropriate equipment for resuscitation. In all cases good environmental control must be maintained to prevent the allergen being dispersed from the test equipment.

8.0 THE MEDICAL SURVEILLANCE PROGRAMME

8.1 The Objective

Medical surveillance is one component of an occupational health programme which should seek to promote and maintain the health of all employees at the given workplace, who are at risk of developing adverse health effects resulting from exposure to work place hazards.

In the refining of platinum and handling of platinum compounds, there is a risk of exposure to hazards other than chloroplatinates e.g. chlorine, ammonia, hydrazine, formaldehyde and many others. Many of these may cause adverse health effects or aggravate pre-existing conditions. A high standard of personal hygiene is required and wearing of personal protective equipment is a necessity often including respiratory protective equipment.

The full co-operation of the employee in the medical surveillance programme is essential and requires an understanding and acceptance of the need to disclose symptoms should they occur.

The objectives of the medical surveillance programme for platinum salt exposures should be:

By pre-placement examination:

* Identify pre-existing disease which may be aggravated by the risks at work, or which may mask early signs of ACHSoP.

* Identify pre-existing conditions which may prevent the necessary high standards of personal hygiene.

* Identify the factors which increase the risk of developing ACHSoP.

During employment:

* Identify and assess cases of ACHSoP at an early stage, so that appropriate action can be taken to prevent the development of adverse health effects.

8.2 Pre-placement Examination

The components of the pre-placement examination include:

* Occupational history, in particular enquiry about previous exposure to platinum salts and respiratory sensitisers or irritants.

* Medical history, with particular enquiry for previous respiratory disease and indications of atopy, medication e.g. beta blockers which may aggravate an asthmatic reaction.

* Physical examination.

* Spirometry.

* Skin Prick Test with
  - common allergens appropriate to local environment
  - Na_2PtCl_6 10^{-3}g/ml 0.9% NaCl - if prior exposure has occurred or is suspected.

8.3 Criteria for Employment

Selection of employees for work with allergenic platinum salts requires that they be free from pre-existing disease which may be aggravated if they develop ACHSoP, they should not be susceptible to the effects of associated occupational hazards and should be fit to comply with the local safety and hygiene requirements.

Risk factors which increase the risk e.g. smoking may be significant if there is a high incidence of ACHSoP in the existing workforce.

Criteria for and contra-indications to employment need to be considered with respect to anti-discrimination legislation. This will require a full evaluation of risk, the increase in risk due to particular factors or the effect on the health of the individual who may develop ACHSoP. Factors to be considered will normally include:

* Allergy to complex salts of platinum from previous work. This is an absolute exclusion.

* Asthma, as bronchial hyperresponsiveness would be expected to be aggravated by ACHSoP and existing asthma would mask the development of ACHSoP.

* Chronic respiratory disease with FVC or FEV_1 2SD or more below predicted values (normally 1 litre below normal). Local predicted values should be used e.g. ECCS in Europe. FEV_1 /FVC should normally exceed 70%.

* Allergic rhinitis may make it difficult to maintain the necessary standards of hygiene.

* Skin disease e.g. dermatitis, neuro-dermatitis, or severe psoriasis, which would prevent adequate washing and showering.

* Skin disease e.g. chronic ulceration which provides a portal of entry to surface contamination. The use of an insulin perfusor for treatment of type 1 diabetes may be incompatible with hygiene requirements.

* Disease which requires frequent medication, food or fluid may be incompatible with maintenance of hygiene standards.

* Smoking and atopy as contraindications may be considered in terms of risk relative to the risk of sensitisation in the absence of these factors.

8.4 **Examination During Employment**

A follow up study of ACHSoP showed that if exposure to the chloroplatinates ceased within 12 months of developing symptoms there was a subsequent decline in symptoms and bronchial hyperresponsiveness [21]. Another study showed that when there was an immediate cessation of exposure following diagnosis of the allergy there was no significant difference in the incidence of bronchial hyperresponsiveness between the cases and matched employees who left without the allergy [19]. This indicates that medical examination should be conducted at least every 12 months. More frequent testing may be recommended according to local circumstances. As with other occupational asthmas, most cases occur within the first 2 or 3 years of exposure [40] and more frequent testing during these years may be appropriate.

Subjects under surveillance should be aware of the symptoms of ACHSoP and the significance of persistence of the symptoms so that they will report them should they occur in between routine tests and allow proper investigation.

The routine tests include:

* Questionnaire for symptoms of ACHSoP.

* Review of recent medical history.

* Spirometry

* SPT with Na_2PtCl_6 at 10^{-3}g/ml

Other tests may be performed to promote good health but do not contribute to the early recognition of ACHSoP. It is common to include annual physical examination.

8.5 **Diagnostic Criteria**

Cases of ACHSoP may be identified at all stages of the disease at routine surveillance examination or in the intervals between them. Further investigation and management of cases after first presentation or detection may vary according to local or national requirements for compensation or labour agreements.

Non-pulmonary, nasal, ocular or dermal symptoms may require special investigation. Nasal symptoms may be investigated by specific challenge to measure mucus flow rates, nasal obstruction or eosinophil in mucus. Urticaria is an obvious response to direct skin contact and is confirmed by SPT or contact. Contact dermatitis is confirmed by patch test.

There is no internationally agreed scheme for reporting ACHSoP because of the various national and local requirements for investigation, reporting and compensation. Until there is an agreed format which will allow for comparison, medical records should show:

* Skin prick test reaction and size of response at serial dilution.

* Symptoms and organ affected ie eye, nose, chest, skin.

* Spirometric change in relation to exposure.

* Non specific hyperresponsiveness if tested.

* Response to specific challenge if tested.

Following confirmation of the diagnosis of ACHSoP cases with minor symptoms may be accommodated with more stringent medical surveillance and reduced exposure. Increased bronchial hyperresponsiveness due to ACHSoP indicates a need to cease exposure.

8.6 **Post Exposure Examination**

It can be anticipated that the symptoms of ACHSoP will decline when exposure ceases. Continued medical surveillance would not be expected to affect the outcome. However, because of the different experiences in follow up studies, prospective study of all cases is to be recommended with review suggested after 3 and 12 months with continued follow up when possible.

9.0 APPENDIX

9.1 References

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9.2 **Abbreviations**

ACHSoP	Allergy to the complex halogeno salts of platinum
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GCS	Glycerol carbol saline
HSA	Human serum albumen
IgE	Immunoglobulin E
NSBH	Non-specific bronchial hyperresponsiveness
PBS	Phosphate buffered saline
PC_{20}	The concentration of inhaled challenge substance provoking a 20% reduction of FEV_1
PD_{50}sGaw	The dose of inhaled challenge substance provoking a 50% reduction of specific airway conductance
PEFR	Peak expiratory flow rate
RAST	Radio allergo sorbent test
sGaw	Specific airway conductance
SPT	Skin prick test

9.3 Calculation of Incidence and Risk

Incidence rates of ACHSoP may be reported as absolute numbers e.g. x cases per annum or related to employee months e.g. as y per 100 employee months. The latter method takes account of fluctuations in personnel number and is a better reflection of trends.

ACHSoP as with other occupational allergies only affects a proportion of those exposed and does so in the first years of work. As a result a long established facility will tend to employ "survivors" and have a low incidence rate. The incidence rate may not give an accurate reflection of risk for new starters in the workplace.

As the risk of developing ACHSoP is highest in the first 2 or 3 years it is possible to determine cumulative risk for a group of new starters in a workplace and follow their progress for 2 (or 3) years. Survival curves for new starters with a risk factor e.g. smoking or atopy can be compared with the curves for those without. (Berksen & Gage 1959) or regression curves may be calculated.

If the groups being compared are comparable in other aspects the relative risk for a particular factor may be calculated by use of a 2 x 2 (4 fold) table.

		Disease		
		Positive	Negative	Total
Variable	Positive	a	b	a + b
	Negative	c	d	c + d
	Total	a + c	b + d	a + b +c + d

The rate for subjects with the risk factor Re = a / (a + b)
The rate for subjects without the risk factor Ro = c / (c + d)
The Relative Risk or Risk Ratio RR = Re / Ro

The Rate Difference, Risk Difference or Attributable Risk AR = Re - Ro

The reciprocal of Attributable Risk (1 / AR) gives the number of subjects with particular risk factor who would have to be excluded from exposure in order to prevent one case (NNE).

Once sufficient numbers of subjects have been observed for 2 or 3 years, the rate Ro can be calculated for that group of new starters. Using previously published RR for smoking or atopy - or those from the workplace being studied Ro, Re, RR, AR and NNE can be calculated to decide whether smokers or atopics should be excluded.

In general when rates are low exclusion is not warranted but may be justified when rates are high.

9.4 Protocol for Preparation of Test Solution

(i) Preparation of Stock Solution

Weigh 1g of Na_2PtCl_6
Dissolve in 0.9% NaCl and make up to 100 ml.

This is the stock solution for future dilutions. It is stable but should be stored in the dark and refrigerated.

(ii) Preparation of Serial Dilutions

Set up 7 small bottles labelled 10^{-3}, 10^{-4}, 10^{-5} , 10^{-6}, 10^{-7}, 10^{-8}, 10^{-9} g/ml.
Deliver 9.0ml of 0.9% NaCl solution into each bottle.
Pipette 1.0ml of stock solution (10^{-2} g/ml) into the bottle labelled 10^{-3} g/ml.
Stopper and shake well.
Pipette 1.0 ml of 10^{-3} g/ml solution and add to the bottle labelled 10^{-4} g/ml.
Stopper and shake well.
Continue - diluting in sequence to produce 10^{-9} g/ml.

The diluted solution may be dispensed into small bottles for ease of use.

(iii) Control Solutions

The diluent 0.9% NaCl is used as the negative control.
Histamine phosphate 10% may be used as a positive control.

(iv) Phosphate Buffered Saline (PBS)

.

When solutions are to be used for inhalational challenge, PBS should be used in place of 0.9% NaCl for all dilutions and as the negative control.

The formula for PBS is:

NaCl	137 mmol	(8.006g per litre)
KCl	3 mmol	(0.224g per litre)
Na_2HPO_4 $12H_2O$	8 mmol	(2.865g per litre)
KH_2 PO_4	1.5 mmol	(0.204g per litre)

(v) Disposal of Surplus and Waste Solution

Excess and redundant test solutions should be treated to reduce the chloroplatinates to non-allergenic compounds before disposal. Solutions and contaminated surfaces may be treated with sodium borohydride solution for this purpose.