IPA

INTERNATIONAL PLATINUM GROUP METALS ASSOCIATION

MEDICAL SURVEILLANCE OF WORKERS EXPOSED TO RESPIRATORY SENSITISING PLATINUM COMPOUNDS

CONTENTS

SUMMARY

- This chapter mainly focuses on methods and standards for investigating, diagnosing, and managing respiratory sensitisation in platinum workers.

- Workers within PGM industries – most notably those exposed to CHPS – can develop platinum salt sensitivity (PSS); see Chapter 6 for detailed coverage of the toxicology, clinical features, and risk factors of PSS.

- The principal tools for surveillance, investigation and diagnosis of PSS include questionnaires for assessing clinical symptoms, objective tests of immunological response (IgE) to confirm sensitisation to CHPS, and respiratory function tests to confirm or exclude occupational asthma.

- Skin prick testing (SPT) using a standard solution of sodium hexachloroplatinate, Na_2PtCl_6, is a sensitive, specific and cost effective way to test for sensitisation to platinum salts. Depending on the specific statutory requirements and conditions of the respective jurisdictions, it can be the method of choice for surveillance of exposed workers and can be used by physicians or nurses within an occupational setting. The standard solution for screening is typically Na_2PtCl_6 at an initial concentration of 10^{-3} g/ml in 0.9% NaCl solution.

- Based on current knowledge, long-term surveillance using sodium hexachloroplatinate for SPT on control subjects otherwise unexposed to chloroplatinates has not resulted in cases of induced sensitisation.

- Respiratory function tests concentrating on the measurement of volume and flow by spirometry are used for routine surveillance, to assess acute symptoms at work and for across-shift and peak-flow monitoring. It is important to maintain high standards of equipment and performance, as well as well-trained personnel, in conducting spirometric

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measurements.

- In instances when SPT occasionally fails to identify symptomatic workers, it may be appropriate to conduct bronchial challenge tests. Such tests should only be carried out by experienced physicians or clinicians in specialised clinics outside the workplace.

- Any specific medical surveillance programme should be developed in consultation with properly trained medical and occupational health professionals. The invasiveness, safety, sensitivity, and accuracy of testing procedures in compliance with the legal requirements in the respective jurisdictions must be carefully considered, as should the rights of workers and laws regarding discriminatory practices, recordkeeping and the privacy of medical records.

- Surveillance programmes should include: a pre-placement examination, during which previous exposures to CHPS, respiratory sensitisers or irritants, and any history of respiratory disease or smoking is investigated; periodic assessments (physical examinations, SPT and spirometry); and an examination on termination of employment.

- Prevention and intervention strategies for managing PSS will be unique to each facility or jurisdiction. However, early diagnosis – via the investigations and examinations described above – is considered to be the most critical objective of any effective medical surveillance management programme.

- Due to the special circumstances of their exposures to platins and other antineoplastic agents, medical surveillance guidelines for health care workers have been developed by individual government agencies and/or medical societies. Readers should refer to local jurisdictional information.

Note: Due to constantly evolving legal conditions and requirements readers must verify compliance with applicable local regulations related to worker medical surveillance.

7.1

DETERMINING WORKERS AT RISK AND RISK FACTORS

As noted in Chapter 6, workers at risk of developing respiratory sensitisation mainly comprise those exposed to CHPS[1] in industrial settings such as refining operations; certain catalyst manufacturing, electroplating, and electrolysis operations; and within miscellaneous occupations (*e.g.*, chemists, technicians). CHPS typically do not occur outside the workplace and, thus, respiratory sensitisation is largely of concern solely within these occupational settings.

However, as further described in Chapter 6, health care workers (HCWs) may also constitute a potential group of "at risk" workers for respiratory sensitisation due to their exposures to platinum-containing anticancer drugs (*i.e.*, "platins"). To date, respiratory sensitisation has not been reported in HCWs, but it has been observed—along with other adverse health effects—in patients infused with platins. Due to this potential for sensitisation, the medical surveillance programmes defined for workers exposed to CHPS, and discussed below, are also considered to be applicable to production workers and HCW handling platins.

In contrast to the above groups, respiratory sensitisation has not been observed in workers exposed only to elemental platinum or other platinum compounds (see Chapter 6; Section 6.2). As such, these workers have not been considered "at risk" for respiratory sensitisation within the context of this Chapter, bearing in mind that this Guide reflects current knowledge that may be subject to change based on future research. However, medical surveillance for other health risks within these workers may be appropriate.

The sensitisation reactions caused by CHPS and platins are believed to be humoral immune responses, typically associated with increased levels of IgE, and thought to be linked to an initial Th2-type cytokine release (see Section 6.3 for a detailed discussion). Respiratory sensitisation seen in CHPS workers are typically Type I (IgE) immediate-type hypersensitivity reactions which are characterised by a symptom-free latency period and increased sensitisation over time, with sensitized subjects reacting to lower exposure levels (elicitation) than the levels required to induce sensitisation. Likewise, sensitisation reactions in platin-infused patients are mainly thought to be Type I IgE reactions, although Type II, III, and IV reactions have also been observed (Makrilia *et al.*, 2010). Typically, platin-induced allergic reactions are not seen in patients until several cycles of drug treatment have been administered.

While occupationally-related respiratory sensitisation may be *induced* via inhalation, dermal contact, or a combination of both, it is believed that *elicitation* responses in the respiratory system require inhalation exposure to a sufficient quantity of the inducing agent (Arts *et al.*, 2006; Cochrane *et al.*, 2015). This may account for why respiratory sensitisation has not been observed to date in HCWs (see Section 7.5, page 19 for further discussion). As an alternative explanation, HCWs may typically not absorb sufficient platin to induce a sensitisation response.

Although all CHPS-exposed workers should be considered "at risk" for respiratory sensitisation, it is important to note that a minority of CHPS-exposed workers become sensitised[2]. As with other occupational allergies, platinum salt sensitivity (PSS) affects only a proportion of those exposed and usually does

[1] Complex halogenated platinum salts (CHPS) are compounds where the halide is directly coordinated to a central Pt atom.

[2] Synonymous with platinum salt sensitisation.

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so within the first two to three years of exposure. As a result, long-established facilities will tend to employ "survivors" with sensitised workers having either been removed from potentially hazardous exposure settings or terminated from employment. Current incidence rates of skin prick test (SPT) conversion are generally below 5 per 100 person years of exposure (Heederik *et al.*, 2016) and are considerably lower than those reported up to the mid-1980s.

Genetics may also constitute a risk factor (Newman-Taylor *et al.*, 1999). On the whole, the preponderance of evidence suggests that cigarette smoking and genetic factors may constitute greater risk factors than atopy, gender, or pre-existing non-specific bronchial hypersensitivity in the development of chemical respiratory sensitisation (Cochrane *et al.*, 2015). Any concomitant risk factors taken into account in designing medical surveillance programmes for CHPS-exposed workers should be in accordance with local/national employment guidelines (see Section 7.5).

7.2

INVESTIGATIVE AND DIAGNOSTIC TECHNIQUES FOR PSS

PSS is a clinical condition in which characteristic symptoms occur (described below). A diagnosis of PSS should never be made on the basis of history alone (Fishwick *et al.*, 2008). Rather, it should be confirmed by an assessment of the relationship of the observed symptoms to the work being done and further supported by tests of immunological response and objective measurements of respiratory effects. It should be noted that a number of tests that have been used to investigate PSS—including specific inhalation challenge (SIC) with chloroplatinate salts, and tests for measurement of non-specific bronchial hyperresponsiveness (NSBHR)—will not be routinely available for use by most occupational physicians responsible for medical surveillance, as such tests are usually available only in specialised research laboratories. In the review that follows, the various routines and tests described are discussed relative to their practical use in establishing an effective medical surveillance programme within the workplace.

The methods for investigation and diagnosis of PSS may be considered under three subheadings:

- Clinical features.
- Immunology.
- Respiratory function.

These are discussed in more detail below.

While biological monitoring for systemic absorption of Pt has been conducted in workers, no predictive correlation has been established with respect to Pt found in biological media and risk of sensitisation (Merget *et al.*, 2002; Petrucci *et al.*, 2005; Kiilunen and Aitio, 2007; see Chapter 5 for further discussion). Some regulatory bodies have proposed the use of platinum urinary levels as potential indicators of workplace exposures, but they have cautioned that such levels are not necessarily related to health risks (ASU, 2013). Users of this Guide are advised to consult with appropriate regulatory authorities regarding jurisdictional requirements, if any, for biological monitoring.

CLINICAL FEATURES

Although previously discussed in Chapter 6, it is worth reiterating that the signs and symptoms constituting the clinical features of the allergic responses seen in CHPS-exposed workers include:

- Conjunctivitis with itching and lacrimation.
- Pruritis and/or skin rash.
- Rhinitis with nasal obstruction, rhinorrhoea, sneezing attacks.
- Bronchial/asthma-type effects including cough, tightness of the chest, wheezing and shortness of breath.

These features, while not specific to CHPS, are referred to as “platinum salt sensitivity” (PSS) when observed in the context of CHPS exposures. Symptoms occur within a few minutes of exposure at the workplace in sensitised individuals and are typically absent over weekends or other periods when not at work. Symptoms usually resolve spontaneously (sometimes without treatment) on removal from exposure. While

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conjunctivitis and rhinitis are often the first signs in the clinical manifestation of PSS (Stoughton *et al.*, 2008), it is not uncommon for cases to present with occupational asthma at the time skin prick test conversion is first observed. Occasionally the asthmatic response may be delayed and cause nocturnal respiratory symptoms. Contact urticaria may occur on direct contact with CHPS.

The methods for investigating the clinical features of PSS noted above typically take the form of standardised questionnaires. Both clinical setting questionnaires and free histories taken by experts to identify work-related symptoms of occupational asthma have high sensitivity but low specificity (Nicholson *et al.*, 2005). Standardised questionnaires for respiratory symptoms have been validated (Burney *et al.*, 1984; Liard and Neukrich, 2000) and are useful in cross-sectional surveys and initial and follow-up examinations. Indeed, in certain jurisdictions, they may be required and prototypes have been provided by regulatory authorities (ASU, 2013). However, in other jurisdictions, regulatory authorities have found that standard questionnaires may be too lengthy when specific work-related symptoms need to be assessed at regular intervals (HSE, 1994). In such instances, abbreviated forms may be used (HSE, 1994).

It is therefore important that users of this Guide consult with appropriate regulatory authorities regarding jurisdictional requirements.

Self-administered questionnaires are subject to recall bias, *i.e.*, those with a medical condition are more likely to report their exposures compared to those without the condition. As such, they should only be used when other options for querying the worker are unavailable. Positive answers to any questionnaires should be explored fully to assess relationships to work. Upper respiratory symptoms are common in the general population (HSE, 1994) 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 occupational settings where it is known that a diagnosis of occupational asthma requires removal from exposure, symptoms have occasionally been denied initially by subjects on routine questioning. However, when the symptoms are of such severity that the worker acknowledges the need to cease exposure, long-standing symptoms are often ultimately admitted to by the worker. This indicates a need to support the use of questionnaires by studies of immunology and lung function.

IMMUNOLOGY

As noted above, the sensitisation reactions caused by CHPS are believed to be humoral immune responses (*i.e.*, Type I allergic reactions) typically associated with increased levels of IgE. Thus, tests for the detection of antibodies have been directed towards measurement of total IgE and specific IgE in serum (Cromwell *et al.*, 1979). However, the pre-eminent investigative strategy currently in use is the detection of specific IgE in skin via direct challenge using the skin prick test (SPT).

SPECIFIC AND TOTAL IGE

High levels of specific IgE measured by radioallergosorbent test (RAST) correlate with SPT reaction, but SPT may be positive with low levels of specific IgE to platinum (Cromwell, 1979). There is poor correlation with symptoms. The RAST for specific IgE is complex and slow and has not been helpful in establishing a diagnosis when the SPT has remained negative. A correlation of specific IgE with total IgE has been found making the interpretation difficult in subjects with high total serum IgE (Merget *et al.*, 1988; Calverley *et al.*, 1999).

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SKIN PRICK TEST (SPT)

While skin testing methods for investigation of allergies have included intradermal, scratch, and prick tests (Pepys, 1975; Nelson, 1983), 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. Depending on the specific statutory requirements and conditions of the respective jurisdictions, it is the recommended method for serial observation for the development of sensitivity to platinum salts that can be used by the occupational medical practitioner (OMP) within an occupational setting to demonstrate the presence of specific IgE.

TESTING SOLUTIONS

The salt:
Early studies of platinum refinery workers used three platinum salts:

Note: The usage of the methods and testing procedures described here remains under the sole responsibility of the user. The invasiveness, safety, sensitivity, and accuracy of testing procedures in compliance with the legal requirements in the respective jurisdictions must be carefully verified by readers in each individual case in advance.

ammonium hexachloroplatinate [$(NH_4)_2PtCl_6$], sodium hexachloroplatinate [Na_2PtCl_6], and sodium tetrachloroplatinate [Na_2PtCl_4]. In the majority of cases of PSS there are positive responses to all three salts. Chloroplatinic acid [H_2PtCl_6] is not recommended as its low pH may cause false positive skin reactions if used for SPT.

Due to its high stability it is usually recommended to use one salt, namely Na_2PtCl_6, for routine surveillance and as the standard for subsequent studies. If symptoms strongly suggest PSS and the SPT using Na_2PtCl_6 is negative, then SPT using the other complex salts may be indicated to confirm the diagnosis of PSS.

The diluent:
Previously 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. IPA member companies agreed in 2002 to adopt sodium hexachloroplatinate in 0.9% sodium chloride as diluent for SPT solutions.

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 inhalation 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 as the salt have been established as safe, and do not provoke reactions in non-exposed subjects (Cleare *et al.*, 1979). Solutions with higher concentrations, *e.g.* 10^{-2} g/ml, may cause non-specific histamine release in skin (Cleare *et al.*, 1976). Mild systemic reactions have been reported in *symptomatic* individuals when solutions containing 10^{-2} mol/litre [4.86 x 10^{-3} g/ml] were used for SPT (Merget *et al.*, 1991b).

Concerns have been expressed as to whether SPT could induce hypersensitivity to platinum salts. SPT using 10^{-3} g/ml introduces 3 x 10^{-6} ml into the epidermis (Squire, 1952) giving 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 (Kulzer *et al.*, 1995; Merget *et al.*, 2000).

It is recommended that the standard solution for SPT testing should be Na_2PtCl_6 at a concentration of 10^{-3} g/ml in 0.9% NaCl solution.

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A protocol for preparation of the test solution can be obtained by contacting IPA (science@ipa-news.com).

Negative control:
A solution of 0.9% sodium chloride (physiological saline) should be used as a negative control for all tests.

Positive control:
Histamine Base solution (1 mg/ml) may be used as a positive control to confirm skin reactivity to allergenic challenge.

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 sterile 25G disposable needle is introduced at an acute angle to the skin through the drop into the epidermis and lifted gently. A perceptible "plink" 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

The test is read after 15 to 20 minutes; the diameter of the weal is measured and recorded. The size of the flare is not recorded. Weal size can be 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.

An impression can be recorded by outlining the weal in ink (after cleaning the forearm with alcohol), applying transparent or translucent adhesive tape over the test site then lifting off the mark and sticking the imprint to the record.

SPECIFICITY AND SENSITIVITY

Positive SPT reactions have been seen only in people who have had exposure to platinum salts. It is thus 100% specific in subjects who have never been exposed to CHPS (Cleare *et al.*, 1979).

However, false negative tests do occasionally occur in exposed individuals presenting with symptoms of PSS (Calverley *et al.*, 1995; Linnett and Hughes, 1999; Merget *et al.*, 2015). Experience with specific bronchial challenge in such individuals suggests a sensitivity for SPT of about 80-90%. When exposure to platinum salts continues at the same level that caused sensitisation the positive SPT is 100% predictive for development of symptoms (Calverley *et al.*, 1995).

INTERPRETATION OF THE SPT RESULT

A positive SPT is defined as one in which a palpable weal occurs at the test solution prick site measuring 3 mm or greater than any weal occurring at the negative control solution prick site.

A new positive SPT should be confirmed by repeat testing at a follow up examination. Duplicate testing can be done in the case of an equivocal result. Occasional late reactions may occur between 8 and 24 hours later but too few are reported for their significance to have been analysed fully.

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 2 mm diameter or less. Such tests should be followed up with repeat testing. A change in the SPT reaction from negative to a 2 mm diameter weal with a negative control test in a symptomatic individual may be confirmation of PSS if the reaction is consistent and repeatable.

OTHER MARKERS OF ALLERGY

Other investigations of PSS have included measurement of eosinophilia in blood and mucus, as well as histamine release from basophils. Such tests are non-specific and generally do not contribute to the investigation or management of individual cases and are not recommended.

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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.

Note: The invasiveness, safety, sensitivity, and accuracy of testing procedures in compliance with the legal requirements in the respective jurisdictions must be carefully verified by readers in each individual case in advance.

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 CHPS exposure.

EQUIPMENT AND METHODS

High standards of equipment and performance are required. Comprehensive guidance has been published on standardised lung function testing including reference values (Quanjer *et al.*, 2012; Miller *et al.*, 2005). Guidelines have also been prepared for the diagnosis of occupational asthma (EAACI, 1992), and the evaluation of impairment/disability (Pellegrino *et al.*, 2005). Personnel responsible for spirometry should be trained for this and their continuing competence documented.

SPIROMETRY FOR ACUTE SYMPTOMS AT WORK

Spirometric measurements in acutely symptomatic workers provide objective evidence to corroborate symptoms of asthma and to confirm the presence and severity of airflow obstruction when it occurs. 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 coughing, wheezing, chest tightness, or shortness of breath. Spirometry is often difficult to perform under acute

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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. 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.

ACROSS-SHIFT MONITORING

Usually episodes of airflow obstruction at work are acute and well-defined so that the affected individual presents with symptoms. Across-shift monitoring of FEV1 (Forced Expiratory Pressure in 1 Second) may be useful for documenting the frequency and severity of these episodes. Insidious loss of lung function over a work day or work week seldom occurs.

PEAK FLOW RATE MONITORING

The evaluation of peak expiratory flow rate (PEFR) recordings is a widely-used method in the diagnosis of occupational asthma and to confirm the relationship of symptoms 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 4-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 can be 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 intra-day variability at work than at weekends or during holidays (Burge, 1993).

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 inhalation challenge, the sensitivity of PEFR monitoring is 81 to 87% and the specificity 74 to 90% (Perrin *et al.*, 1992).

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

7.4

INHALATION CHALLENGE TESTING

Bronchial hyperresponsiveness describes the narrowing of airways in response to physical or chemical stimuli that normally have little or no effect. Inhalation challenge testing to measure either non-specific bronchial hyperresponsiveness (NSBHR) or specific bronchial hyperresponsiveness may be indicated in the diagnosis of CHPS-related occupational asthma.

Note: The invasiveness, safety, sensitivity, and accuracy of testing procedures in compliance with the legal requirements in the respective jurisdictions must be carefully verified by readers in each individual case in advance.

NON-SPECIFIC INHALATION CHALLENGE TESTING

Inhalation challenge testing for NSBHR using a number of chemical (methacholine, histamine) or physical (cold air, exercise) agents is a widely used procedure in the diagnosis of asthma. It should be noted however that NSBHR may vary over time, increasing during exacerbations (*e.g.* following asthma attacks in response to acute CHPS exposure in sensitised individuals) or decreasing as a result of anti-inflammatory medication (or in the case of PSS, following CHPS exposure avoidance). Methacholine challenge testing (MCT) is the most widely used method for assessing NSBHR and when used alone, is considered more useful in excluding a diagnosis of asthma than in establishing one because its negative predictive power is greater than its positive predicted power (ATS, 1999). However, a negative MCT in a symptomatic worker exposed to CHPS does not necessarily exclude a diagnosis of CHPS-associated occupational asthma (Anees *et al.*, 2002). Changes in NSBHR at and away from work have only moderate sensitivity and specificity for a diagnosis of OA (Fishwick *et al.*, 2008). Most studies however have failed to demonstrate a clear relationship between the changes in NSBHR and specific reactivity to occupational agents (Vandenplas *et al.*, 2014).

SPECIFIC INHALATION TESTING

Specific inhalation challenge (SIC) testing is considered a “reference standard” for the diagnosis of occupational asthma (Beach *et al.*, 2007) although both false negative and false positive results may occur (Vandenplas *et al.*, 2014). Two methods for SIC testing in CHPS-exposed workers are routinely used, one mimicking workplace exposure using dry particulate $(NH_4)_2PtCl_6$ suspended in lactose (Pickering,

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INHALATION CHALLENGE TESTING

1972) and one using a nebulized solution of Na_2PtCl_6 (Merget *et al.*, 1991b; Merget *et al.*, 2015). As performance of these tests is beyond the capabilities of most companies, the methodology is not further discussed in this Guide; but indications for SIC testing in CHPS-exposed workers are given below (Section 7.4, page 14).

Due to the possibility of severe asthmatic or anaphylactoid reactions, specific challenge tests in particular should only be performed according to standardised procedures within specialised clinics (Vandenplas *et al.*, 2014; ASU, 2013).

INDICATIONS FOR SPECIFIC INHALATION TESTING

A diagnosis of occupational asthma may be made with a high degree of certainty in the case of a CHPS-exposed worker, with no previous history of asthma, presenting with appropriate work-related symptoms of PSS as described above, confirmed positive platinum SPT and documented episodes of reversible airflow obstruction demonstrated by spirometry. However, in instances when routine objective methods fail to provide a definitive diagnosis (Calverley *et al.*, 1995; Linnett and Hughes, 1999), SIC may be indicated depending on the desired level of diagnostic accuracy required (which may be different for clinical or compensation purposes and may vary between jurisdictions and different countries (Vandenplas *et al.*, 2014)).

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MEDICAL SURVEILLANCE PROGRAMMES AND CASE MANAGEMENT

MEDICAL SURVEILLANCE PROGRAMMES AND CASE MANAGEMENT

It should be borne in mind that any medical surveillance programme specific to a particular facility should be developed in consultation with appropriate medical and occupational health professionals. Considerable clinical skill and judgment are required in implementing such programmes and consultation with properly trained personnel is critical. As noted in the previous section, issues such as the invasiveness, safety, sensitivity, and accuracy of testing procedures in compliance with the constantly evolving legal conditions and requirements in the respective jurisdiction must be considered carefully, as should the rights of the workers. Laws regarding discriminatory practices in hiring and job placement should be strictly followed, as should regulations on recordkeeping and privacy of medical records. Any health data gathered and recorded should be subject to rigorous quality control. In countries where implementation of a medical surveillance programme is obligatory, company-based surveillance programmes should be in compliance with the relevant local/national guidelines and applicable statutory requirements.

MEDICAL SURVEILLANCE OF CHPS-EXPOSED WORKERS

Medical surveillance is one component of an occupational health programme which should seek to protect and maintain the health of all employees at the given workplace who are at risk of developing adverse health effects resulting from exposure to workplace hazards (see also Chapters 8-10).

In the refining of platinum and handling of platinum compounds, there is a risk of exposure to hazards other than CHPS (*e.g.*, acid mists, chlorine, ammonia, hydrazine, formaldehyde and other chemical agents). 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.

A medical surveillance programme should include a pre-placement examination followed by periodic assessments and examination on termination of employment. Periodic assessments may be conducted routinely (*e.g.*, semi-annually, yearly, etc.) or under special circumstances (*e.g.*, when a worker is moved between workplaces with different exposure levels, or if workers suspect a causal link between illness and their workplace exposures, etc.).

The objectives of these examinations should be as follows:

- Identify pre-existing disease which may be aggravated by the risks at work, or which may mask early signs of PSS.
- Identify pre-existing conditions which may prevent the necessary high standards of personal hygiene, or the effective use of personal protective

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equipment such as respirators.

- Identify the factors which increase the risk of developing PSS.
- Identify and assess cases of PSS at an early stage, so that appropriate action can be taken to prevent the development of adverse health effects.

PRE-PLACEMENT EXAMINATION

The components of the pre-placement examination should 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, atopy and smoking habits.
- Physical examination.
- Spirometry.
- SPT with standard platinum salt solution (see 7.2, page 9). SPT for common aeroallergens may be performed to identify atopic individuals.

CRITERIA FOR EMPLOYMENT

Selection of employees for work with CHPS requires that they should not have any pre-existing diseases which may be aggravated if they develop PSS. 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.

Factors known to increase the risk, particularly smoking, should also be taken into account.

Potential 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, and the effect on the health of the individual who may develop PSS. Factors to be considered will normally include:

- Allergy to CHPS from previous work. This is an absolute exclusion.
- Risk of developing work aggravated asthma in subjects with pre-existing asthma, due to non-specific irritant exposure in the refining/factory environment.
- Impaired lung function due to underlying chronic respiratory disease with FVC (forced vital capacity) or FEV1 below predicted lower limit of normal (Quanjer *et al.*, 2012).
- Pre-existing allergic rhinitis may make it difficult to maintain the necessary standards of workplace hygiene.
- Skin disease or other condition which would prevent adequate washing and showering (*e.g.*, dermatitis, neuro-dermatitis, or severe psoriasis) or which provides a portal of entry to surface contamination (*e.g.*, chronic ulceration).

PERIODIC SKIN PRICK TESTING

As described above (7.2, page 9) SPT is the most sensitive test available for detecting sensitisation to platinum salts and can be performed on site. Commonly applied intervals for periodic SPT are as follows:

- Over first two years of exposure when risk for sensitisation is highest—3-6 monthly.
- After 2 years exposure—12 monthly, at time of periodic examination.
- Subjects working in known high risk exposure areas should be tested at 3-6 month intervals to ensure earliest diagnosis of sensitisation.

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MEDICAL SURVEILLANCE PROGRAMMES AND CASE MANAGEMENT

PERIODIC MEDICAL EXAMINATIONS

- Periodic examination should be conducted at least annually and include:
- Review of recent medical history.
- Review for symptoms of PSS.
- Physical examination, if indicated.
- Spirometry, including repeat testing after administration of an inhaled bronchodilator if a greater than 15% fall in FEV1 is present compared to the previous test.

Tests included under periodic assessment would apply also to termination examinations.

DIAGNOSTIC CRITERIA

Cases of PSS may be identified at routine scheduled surveillance examinations 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 confirmation by special investigations available in specialist centres only. Nasal symptoms may be investigated by specific challenge to measure mucus flow rates, nasal obstruction, or eosinophils in mucus. Contact dermatitis is confirmed by a patch test.

There is no internationally agreed scheme for reporting PSS 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:

- Symptoms and organ(s) affected (*i.e.*, eye, nose, chest, skin).
- Skin prick test reaction to standard platinum salt solution.
- Spirometry results measured at work at the time of any symptomatic episodes suggestive of asthma.
- Results of tests for non-specific bronchial hyperresponsiveness, if tested in a specialised clinic.
- Results of specific inhalation challenge to platinum salt, if tested in a specialised clinic.

MANAGEMENT OF WORKERS WITH CONFIRMED PSS

As noted in Section 7.1., PSS is characterised by a number of clinical features that usually start in the upper respiratory tract and eyes and progress to the lower respiratory tract in more severe cases (Stoughton *et al.*, 2008). The general belief is that in the formative stages of disease, the symptoms of PSS will decline when work exposures cease (Assoufi *et al.*, 1997; Merget *et al.*, 2001). But in workers with clear manifestations of bronchial hyperresponsiveness (*i.e.*, those later in the course of disease), as many as half continue to have symptoms of asthma even following medical termination (Baker *et al.*, 1990; Merget *et al.*, 1994, 1999). Thus, on a purely health basis, cessation of exposure to CHPS at early stages of confirmed PSS affords the surest—although, not necessarily the only—means to stem the progression of the disease.

In the event that PSS progresses to occupational asthma, the prognosis for complete recovery decreases (see Section 7.5, page 19). This situation is mirrored by other respiratory sensitising agents, leading to the prevailing view that workers with confirmed occupational asthma induced by such agents should be removed

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from exposure to the agent (Chan-Yeung, 1995; Tarlo *et al.*, 1998; Friedman-Jiménez *et al.*, 2000; Stoughton *et al.*, 2008). This is predicated on the belief that even exposures to very low concentrations of sensitising agents may be capable of eliciting asthmatic responses in certain workers already sensitised to the agent and, more importantly, that continued exposure may lead to chronic, permanent asthma.

However, as is the case with all diseases—occupational or otherwise—the risks of PSS must be weighed against certain societal benefits. To this end it is worth noting that in a study on catalyst and refinery workers, Merget *et al.* (1999) showed a decline in sensitivity and symptoms in workers with confirmed PSS and CHPS-induced asthma, who were transferred to work areas with reduced exposures to CHPS. In a roughly four-year follow-up, such transfers did not result in more unfavourable prognoses in these workers when compared to workers completely removed from exposures. Based upon these results, the authors speculated that—at least within the context of the plants studied and the study design—complete removal of the workers from exposure sources might be delayed for several years until better "alternatives" become available. Merget and his co-workers (Merget *et al.*, 1999; Merget, 2000) suggested that transference to low-exposure areas, at least for a limited period of time, may be an acceptable compromise between the obvious socioeconomic benefits accrued to workers versus the potential adverse health effects workers may experience.

More recently Merget and co-workers (Merget *et al.*, 2017) published a further study on the long-term prognosis of symptomatic PSS in a non-random sample of 96 subjects (including 61 [64%] from the 1999 study referenced above). At the time of this second examination (follow up period median 67 months; range 27 – 113) 92 subjects had already been transferred to jobs with very low or no exposure to platinum salts. Skin prick test responders decreased from 86% to 52%, and there was clear improvement for rhinitis, conjunctivitis and contact urticaria. The number of subjects with asthma symptoms also decreased, but 74 subjects (77%) continued to suffer from asthma and 51 (53%) received asthma medication. Uncertainties associated with this study include: (1) selection bias, *i.e.* if only subjects with more advanced disease are referred for study, or as a consequence of loss to follow up; (2) absence of exposure data for the affected workers; and (3) lack of details on the medical surveillance [specifically, the frequency of skin prick testing]. The authors concluded that there is still a need for prospective studies on the effectiveness of surveillance of workers at risk of occupational asthma due to platinum salts. They suggested that surveillance should include skin prick testing as a primary management approach, and that removal from exposure should be considered irrespective of symptoms. However in respect of the latter recommendation, they stated that based on this study, and others in the literature, evidence is lacking that very low exposures without obvious peak exposures (below 20 ng/m^3) induce symptoms. Therefore, transfers to very low exposure areas within the plants should remain an option for such workers pending any updated future information. The above discussion shows the difficulty in establishing a unified approach for managing confirmed cases of PSS. In his 2000 review article, Merget notes that in South Africa and Germany, prevention of chronic asthma is strongly based on detection of the early stages of PSS (followed by immediate removal from exposure once PSS is confirmed), whereas in the UK, more extensive monitoring is performed in order to locate exposure sources more precisely and to minimize the occurrence of PSS (Merget, 2000).

A number of factors enter into decisions regarding options for managing PSS including socioeconomic impact on the workers (both with respect to medical costs of treatment and the loss of income due to possible termination of employment); the social well-being of the workers; and the jurisdictional ethical, legal, educational, and financial

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obligations of the employer to protect its workforce (Friedman-Jiménez *et al.*, 2000; Stoughton *et al.*, 2008; Baur *et al.*, 2012). Each facility and jurisdiction is unique, requiring its own unique prevention and intervention strategies.

In general, however, it is agreed that early diagnosis—through the institution of the type of regular medical surveillance described above—and removal from exposure are critical components of an effective management programme (Nicholson *et al.*, 2005; Baur *et al.*, 2012). For more guidance on this topic, the reader is referred to a comprehensive review by Baur *et al.* (2012).

TREATMENT

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

PROGNOSIS

As occupational asthma associated with PSS is specific to CHPS exposure at the workplace, it might be expected that removal from exposure would lead to complete recovery. However, this has not always been the experience with occupational asthma due to other sensitising agents, particularly when exposure has continued after asthma has developed (Yeung and Grzybowski, 1985; Pisati *et al.*, 1993).

The same is true for CHPS. Whereas skin test reactivity has been shown to decrease after a period of about five years upon cessation of exposure to CHPS, as many as half the workers with clinical manifestations of asthma continue to have symptoms of asthma even following medical termination (Baker *et al.*, 1990; Merget *et al.*, 1994, 1999). As noted in Section 7.5, page 17, the surest means to prevent episodes of asthma and development of non-specific bronchial hyperresponsiveness is to cease exposures to CHPS as soon as possible after a diagnosis of PSS has been confirmed.

MEDICAL SURVEILLANCE OF PLATIN-EXPOSED HEALTH CARE WORKERS

As noted in Chapter 6, exposure of patients to platins can induce a wide variety of health effects beyond those of respiratory sensitisation. HCWs handling platins are often also concomitantly exposed to other toxic antineoplastic agents, and government agencies and/or medical societies have established high standards of occupational hygiene and protective measures for these workers. Medical surveillance guidelines specific to HCWs have also been developed. For a comprehensive list of global guidelines, recommendations, and regulations for handling antineoplastic agents, including platins, the reader is referred to the U.S. Centres for Disease Control and Prevention (www.cdc.gov/niosh/topics/antineoplastic).

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