Platinum salt sensitivity in refinery workers: incidence and effects of smoking and exposure

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Abstract

***Objective*—To measure the incidence of platinum salt sensitivity (PSS) in refinery workers and examine the influence of cigarette smoking and exposure to platinum salts on sensitisation.**

***Design*—A prospective cohort study with examination of workers at quarterly intervals for 18 months, and again at 24 months.**

***Setting*—A South African primary platinum refinery.**

***Subjects*—78 new recruits, selected by the refinery's usual procedure, without apparent atopy and in good respiratory health.**

***Results*—After 24 months 32 (41%) subjects had been diagnosed PSS and were subsequently medically separated. Twenty two (28%) cases were confirmed by positive skin prick test to platinum salts, 10 (13%) cases were symptomatic but skin prick negative. Incidence of cases per 100 person-months was 1·9 skin prick positive and 0·8 negative. Risk of sensitisation was about eight times greater for smokers than non-smokers, and six times greater for high exposure than low exposure.**

***Conclusion*—Smoking and intensity of exposure were definitely associated with development of PSS. Positive response to platinum salt skin prick test had a 100% positive predictive value for symptoms and signs of PSS if exposure continued.**

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Platinum salt sensitivity (PSS) is well documented and sensitised people may present with asthma, rhinitis, urticaria, and dermatitis.[1-3]

Many studies of PSS have been reported, cross sectional surveys,[4-6] cohort studies[7-9] and a historical prospective cohort study.[10] Their usefulness is limited as cross sectional surveys tended to study a "survivor" population whereas other studies started at a particular event (usually medical separation) and data before exposure and data on unaffected workers were often unavailable. The effects of smoking and exposure intensity have each been explored but a comprehensive study of both influences together has not been reported.

A prospective study design starting at employment was indicated[11] to avoid the limitations described. This study, which examined new recruits to a platinum refinery before employment and at intervals during their period of work exposure, was formulated to meet the following objectives.

(1) To determine the incidence of PSS in recruits who satisfied entry criteria for employment.

(2) To investigate the role of tobacco smoking in the development of PSS.

(3) To examine the effect of level of exposure on sensitisation to soluble platinum salts.

Methods

The study population initially numbered 90, and included all new recruits accepted for permanent or long term employment within the vicinity of the refining process, between January 1986 and June 1987. The usual recruitment procedure of the refinery was used, including a medical examination. A history of chronic respiratory disease, allergy symptoms, lung function below prescribed limits, or a positive response to skin prick test with either platinum salts or common allergens precluded employment. Exclusion of recruits with a positive skin prick test to common allergens has become a practice since it was suggested that atopy could increase the risk of sensitisation to platinum salts.[12]

Written informed consent was obtained from all 90 recruits and they were entered into the study at the start of employment. Participants were subsequently reduced by 12 who left the study before the first examination after the start of employment. The final number of 78 subjects studied consisted of 61 white (60 men, one woman), and 17 black men, 44 subjects were employed in production as process controllers and the remaining 34 were in ancillary services, security, cleaning, maintenance, laboratory, and canteen. No administrative or office staff were included.

During the same period an additional 152 temporary, contract, and office staff were employed but not included in the study. Of these, 28 were office workers, 28 worked for less than three months, for 41 there was no record of exact time worked, and three had possible previous exposure to platinum salts. Records of time worked and ending of employment because of PSS confirmed by positive skin prick test to platinum salt were available for 52 of these 152 workers.

The study design was a prospective cohort

study that examined workers before exposure and at three month intervals thereafter for a period of 18 months, or until they left the refinery, whichever occurred first. A final examination after 24 months was conducted on all subjects still employed.

Data collected at clinical examinations consisted of:

(1) Completion of questionnaire detailing: (a) before exposure—smoking history specified by cigarettes smoked a day, health history, previous work exposure to platinum salts and other potentially hazardous materials, current health particularly of respiratory, skin, and eye symptoms; (b) during exposure—current cigarettes smoked a day, job and sections worked during previous three months; respiratory symptoms (cough, shortness of breath, wheeze), asthma, rhinitis, eye and skin symptoms; onset, severity, and duration of symptoms, any improvement away from the workplace, and whether subject perceived symptoms to be work related.

(2) Lung function tests before and after inhaled β_2 agonist. Bronchospasm was defined as a reduction in FEV_1 of more than 15% compared with before exposure, reversible with time or a bronchodilator.

(3) Skin prick tests with platinum salts and common allergens. These were carried out by the standard method, a superficial prick through drops of allergens placed on the volar surface of the forearm. A weal and flare with induration of more than 2 mm was considered positive. Platinum salts (10^{-3} g/ml) used were sodium hexachloroplatinate, sodium tetrachloroplatinite, and ammonium hexachloroplatinate. Common allergens used were house dust, house dust mite, grass pollen, and Bermuda grass mix supplied by Bayer Miles. Negative controls were used to exclude non-specific reactions.

At three month intervals clinical examinations were carried out by the refinery medical officer, who had access to completed questionnaires and skin prick test results. As well as monitoring symptoms and signs of PSS for the purposes of the study, he was also responsible for the subjects' occupational health care. Results of clinical examinations are not presented.

A diagnosis of PSS was made if the subject had a positive response to skin prick test with platinum salts or symptoms and signs consistent with PSS that, in the opinion of the attending medical officer, were so severe that employment should end on medical grounds. These symptoms and signs included immediate or delayed bronchospasm, rhinitis, eye symptoms, urticaria, or dermatitis in response to exposure to platinum salts.

Subjects were categorised by diagnosis as: (a) PSS sensitive—positive to skin prick test to platinum salts, which confirms sensitisation, (b) PSS symptomatic—diagnosed and employment ended on medical grounds because of symptoms and signs, but negative response to skin prick test with platinum salts, (c) PSS negative—negative response to skin prick test with platinum salts and without symptoms and signs consistent with PSS.

The workplace of the subjects studied was a refinery engaged in the primary refining of platinum group metals. Air concentrations of platinum salts were monitored and recommended occupational hygiene control guidelines were followed,[12] the use of respiratory protection for high risk areas and tasks was enforced. This was an airstream helmet with a high efficiency filter, or a full face mask with double filters, or a sealed mask unit supplied with compressed air, as appropriate.

Conditions at the refinery were such that it was probable that all subjects were exposed to platinum salts to some degree, as has been reported in other platinum refineries.[5] Thus intensity of exposure was categorised as a dichotomous grading of either low or high in each work section of the refinery. Initially refinery management was asked to grade the intensity of exposure in each section from their experience of the refining process. These subjective assessments were validated from the records of the company's environmental monitoring. As this had been done for the information of refinery management in the pursuance of a sound occupational hygiene programme, more samples were taken in high risk sections, and particularly when problems had occurred, to assess and deal with such occurrences. Table 1 shows the percentages of measurements of platinum salts in air from all personal samples taken in 24 work sections for a representative period in 1986 that exceeded the recommended maximum or threshold limit value (TLV) of 2 $\mu g/m^3$ when assayed by the method described by the British Health and Safety Executive.[13] These are included to support the gradings of exposure intensity, they are not an assessment of actual inhaled dose, as measurements did not reflect the protection afforded by respiratory equipment, and bias was exerted by the monitoring strategy of sampling more often in high risk situations.

Subjects were graded as highly exposed if they worked in sections where, at times, the TLV was exceeded (although median air concentration was below the TLV). Maintenance personnel were classified as highly exposed, in view of frequent contact with refining process equipment, often in a breakdown situation when immediate maintenance or disassembly was required. All other non-production staff were classified as exposed at low intensity,

Table 1 Percentage of samples where air concentration of platinum salts exceeded the TLV (2 $\mu g/m^3$), summarised by dichotomous categorisation of exposure and general area.

	Sections (n)	*Total Samples (n)*	*> TLV (%)*
High exposure production areas*	17	566	27
Low exposure non-production services†	7	45	0
Total	24	611	25

*Production areas include maintenance and incinerator; †non-production services = security, canteen and cleaning, messengers, medical centre, laboratories, boilerhouse and changehouses.

Table 2 Characteristics of subjects by PSS category

	Total study group	*PSS sensitive*	*PSS symptomatic*	*PSS negative*
Subjects (n)	78	22	10	46
Production staff	44 (56)	16 (73)*	8 (80)*	20 (43)
Non-production staff	34 (44)	6 (27)*	2 (20)*	26 (57)
Race:				
Black	17 (22)	6 (27)	0	11 (24)
White	61 (78)	16 (73)	10 (100)	35 (76)
Smoking:				
Non-smoker	35 (45)	4 (18)*	4 (40)	27 (59)
Smoker	43 (55)	18 (82)*	6 (60)	19 (41)
1–9 Cigarettes/day	18 (23)	8 (36)	0	8 (17)
⩾ 10 Cigarettes/day	25 (32)	10 (45)	6 (60)	11 (24)
Median Cigarettes/day	3	5	10	0
Exposure:				
Months to outcome:				
Group total	1177	292	123	762
Median	14	12	12	22
Graded exposure:				
Low n (%)	34 (44)	5 (23)*	0	29 (63)
High n (%)	44 (56)	17 (77)*	10 (100)*	17 (37)

*P <0.05 *v* PSS negative.

they were not involved in the refining process, and were at all times in sections where air concentration of platinum salts remained below the TLV.

Subjects were classified as smokers if they smoked as much as one cigarette a day at any time from the date of employment to the end of the study. Median number of cigarettes smoked a day was calculated from information gathered at each three monthly examination.

Outcome was taken as (a) development of positive skin prick tests to soluble platinum salts for workers categorised as PSS sensitive, (b) diagnosis of PSS on symptoms, and end of employment for medical reasons, for PSS symptomatic subjects, (c) end of either employment or 24 month study period, whichever occurred first, for PSS negative subjects.

Statistical significance was based on the Mantel-Haenszel χ^2 test (Fisher's exact two tailed values were used when made necessary by cell size) from "EPIINFO" software.[14] Differences were considered significant where $P < 0.05$. Differences in all characteristics between ethnic groups were examined and none were found to be significant, thus stratification of results by race was not justified. Multivariate analyses were done with Cox's proportional hazards survival regression model, with the assistance of "EGRET" software.[15] Smoking and exposure intensity were both measured as dichotomous variables, (smoker or non-smoker, low or high). Two models were used, one examined the risk of becoming PSS sensitive in which PSS symptomatic people were regarded as negative. The second model examined the risk of developing disease related to platinum salts where only PSS negative people were considered negative. Kaplan-Meier estimates of the probability of the workers remaining negative to skin prick with platinum salts, were done with the same software package.[15]

Results

Of the study population of 78 new recruits employed over a period of 18 months, 32 (41%) were diagnosed as having disease related to platinum salts within two years of employment, and their employment was subsequently ended on medical grounds. Twenty two (28%) developed a positive response to soluble platinum salts on skin prick test and were categorised as PSS sensitive, 10 (13%) were unresponsive to skin prick test but were diagnosed on symptoms and signs as PSS symptomatic, the remaining 46 (59%) were PSS negative.

Table 2 presents characteristics of the study group both as a whole and divided into PSS categories, table 3 presents the number and incidence of cases (or total months worked by PSS negative people) both in total and stratified by exposure intensity, by smoking habits of the workers. For clarity, results for PSS sensitive and PSS symptomatic workers are discussed separately, followed by multivariate analyses.

PSS SENSITIVE

An incidence of 1·9 PSS sensitive cases/100 person-months worked was found. Figure 1

Table 3 Smoking habits and incidence of cases by exposure characteristics in each PSS category

	Non-smokers	*Smokers by median cigarettes/day*					
		Smoker	*1–4*	*5–9*	*1–14*	*15–19*	*⩾ 20*
Total (n)	35	43	9	9	12	8	5
Low exposure (n)	16	18	6	6	3	2	1
High exposure (n)	19	25	3	3	9	6	4
PSS Sensitive:							
Total (n (%))	4 (11)	18 (42)	6 (67)	4 (44)	5 (42)	3 (38)	0
Incidence*	0·7	3·2	3·8	2·5	3·9	3	—
Low exposure (n (%))	0	5 (12)	3 (33)	2 (22)	—	—	—
Incidence	—	1·6	2·5	1·9	—	—	—
High exposure (n (%))	4 (11)	13 (30)	3 (33)	2 (22)	5 (42)	3 (38)	
Incidence	1·3	5·2	8·1	6·3	6·0	5·5	—
PSS Symptomatic:							
Total (n (%))	4 (11)	6 (14)	0	0	1 (8)	2 (25)	3 (60)
Incidence	0·7	1·1	—	—	0·8	2·0	10·0
Low exposure (n (%))	0	0	—	—	—	—	—
High exposure (n (%))	4 (11)	6 (14)	—	—	1 (8)	2 (25)	3 (60)
Incidence	1·3	2·4	—	—	1·2	3·6	11·1
PSS Negative							
Total (n (%))	27 (7)	19 (44)	3 (33)	5 (56)	6 (50)	3 (38)	2 (40)
Total months worked	476	286	64	107	58	51	6
Low exposure (n (%))	16 (46)	13 (30)	3 (33)	4 (44)	3 (25)	2 (25)	1 (20)
Total months worked	294	238	64	83	43	45	3
High exposure (n (%))	11 (31)	6 (14)	0	1 (11)	3 (25)	1 (13)	1 (20)
Total months worked	182	48	—	24	15	6	3

*Incidence calculated as cases/100 person months worked.

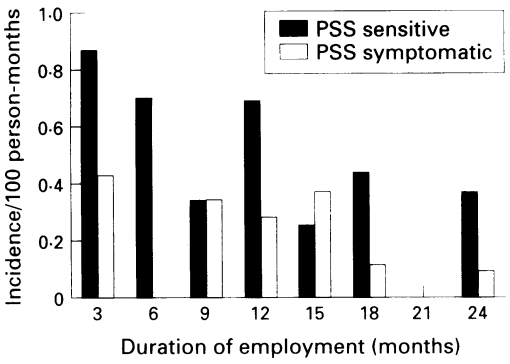

Figure 1 Crude incidence of PSS sensitive and PSS symptomatic cases/100 person-months.

shows that crude incidence did not increase with increasing duration of exposure, cases occurred at a higher rate after three months than after 24 months of employment (0·9 *v* 0·4 cases/100 person-months, respectively).

All 22 PSS sensitive subjects eventually developed symptoms and signs that led to the end of their employment on medical grounds. In 12 cases this occurred simultaneously with first positive skin prick reaction to platinum salts, and in the remaining 10 cases between one and 20 months (median 8·5 months) after first skin prick response. Thus, in this study, skin prick tests to platinum salts had a 100% positive predictive value for end of employment on medical grounds when exposure continued.

Table 2 shows that PSS sensitive workers were employed more frequently in production capacities (73%) than PSS negative workers (43%) P = 0·025, and thus more were graded as highly exposed (77% *v* 37%, P = 0·002). Proportionally twice as many PSS sensitive workers smoked, than did the PSS negative workers (82% *v* 41%, P = 0·002), but the fact that more were heavy smokers (45% PSS sensitive *v* 24% PSS negative) was not significant.

This apparent association with both smoking and exposure and PSS sensitive cases was confirmed when exposure data were stratified by smoking for the three PSS categories. Table 3 shows that among subjects at high exposure a significantly larger proportion, 30%, of the PSS sensitive group were smokers, compared with 14% of the PSS negative group (P = 0·017). In subjects exposed at low intensity all 16 non-smokers remained PSS negative, as did 13 of the smokers, only five were PSS sensitive (P = 0·046). Incidence of cases/100 person-months worked (by subjects in specific smoking categories) indicated that in general non-smokers withstood exposure longer than smokers (0·7 *v* 3·2 cases/100 person-months). High exposure led to an incidence at least three times higher than low exposure across all smoking categories (5·2 *v* 1·6 cases/100 person-months among all smokers). Among smokers an increase in median number of cigarettes smoked a day did not increase the incidence of PSS sensitive cases.

The 52 workers not included in the study worked for a mean of 14 months, there were 11 PSS sensitive cases (that occurred at a median of eight months), a crude incidence of 1·5 cases/100 person-months. Nine of these affected workers were smokers with high exposure, one was a smoker with low exposure, and the 11th a non-smoker with high exposure.

PSS SYMPTOMATIC

All 10 subjects in this group were released from work on medical grounds on a diagnosis of PSS. Symptoms and signs seemed to be work related and included asthma confirmed by lung function tests in seven cases, the three unconfirmed cases had all required medical attention for symptoms and signs of asthma. Crude incidence of PSS symptomatic cases was 0·7/100 person-months worked. A median of 12 months was worked before diagnosis and incidence of new cases at three month examinations declined over time (fig 1).

Comparison of smoking characteristics (table 2) shows that in the PSS symptomatic group the proportion of smokers (60%) closely reflects that of the whole study population (55%), but the proportion of heavy smokers (60%) was higher than in any other group. Exposure characteristics (table 2) show that these PSS symptomatic subjects, compared with PSS negative subjects, were all graded as exposed to a high intensity of platinum salts (100% *v* 37%, P= 0·0002). Intensity of exposure thus was a major predictor of PSS symptomatic cases. Among smokers incidence was shown (table 3) to increase with median number of cigarettes smoked a day. The highest rate, 11·1 PSS symptomatic cases/100 person-months, was recorded for subjects with high exposure who smoked 20 or more cigarettes a day, and accounted for three of only four such subjects included in the study population.

MULTIVARIATE ANALYSIS

The independent effects of smoking and exposure were measured by multivariate analysis. Table 4 shows that from the results presented (with confidence intervals (CIs)) the risk of becoming PSS sensitive was eight times greater in smokers than non-smokers (adjusted for exposure), and six times greater at high than low intensity of exposure (adjusted for smoking). For employment to end on medical grounds a diagnosis of either PSS sensitivity or symptoms exposure was more important, the risk being nine times greater at high than low exposure.

The Kaplan-Meier model (fig 2) graphically presents the probability of workers, in different smoking and exposure categories, surviving employment without becoming PSS sensitive, thus PSS symptomatic workers are regarded as negative. No non-smoking worker with low exposure developed a positive skin prick test to platinum salts within the two years (survival

Table 4 The effects of smoking and exposure category on the risk of becoming PSS sensitive specifically, or PSS (sensitive or symptomatic)

	n	*Hazard ratio (95% CI)*	*P value*
PSS sensitive:	78		
Smoking		8·0 (2·6–25·0)	< 0·001
Exposure		6·2 (2·2–17·7)	< 0·001
PSS (sensitive or symptomatic):	78		
Smoking		5·3 (2·3–12·6)	< 0·001
Exposure		9·0 (3·5–24·3)	< 0·001

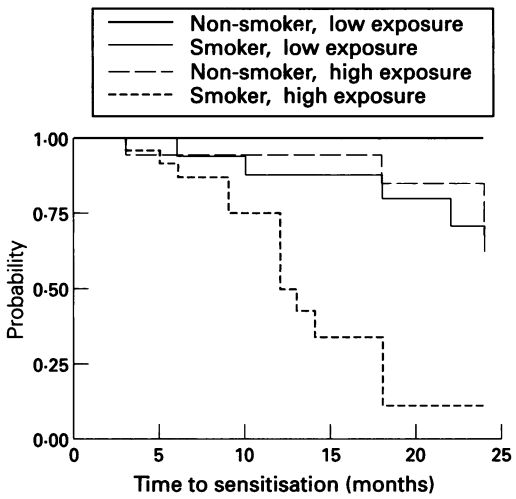

Figure 2 Probability of refinery workers remaining skin prick negative, by smoking and exposure categories.

probability = 1·00 or 100%). In contrast, smokers with high exposure had the worst 24 month survival probability, only 0·114. In general smokers were diagnosed after shorter service than non-smokers; 16 of their 18 failures (89%) had occurred by 18 months of employment, compared with only two of the four failures (50%) of the non-smokers.

Avoidance of the end of employment on medical grounds due to disease related to platinum salts overall (PSS sensitivity or symptoms) is not illustrated, but probabilities for workers in the high exposure group declined to 0·445 (at 24 months) for non-smokers and 0·052 (at 18 months) for smokers.

Discussion

The main objectives of the study were to investigate the incidence of sensitivity to platinum salts and the influence of smoking and exposure. Incidence of disease related to platinum salts (leading to subsequent medical ending of employment) within 24 months, was high, 2·7 cases/100 person-months, or 41% of apparently non-atopic, healthy recruits. Most of the 22 PSS sensitive cases, confirmed by positive skin prick test occurred within 12 months of employment. The study population seems to be representative of the workforce as a whole, incidence of PSS sensitive cases among workers not included was comparable (1·5 *v* 1·9 cases/100 person-months). Our findings were similar to those in the only prospective study available for comparison, the historical cohort study of Venables *et al*,[10] where incidence of sensitisation for the first 24 months was 3·1 cases/100 person-months for workers recruited in 1973–4. The lower incidence of sensitisation of 1·9 cases/100 person-months in our study was predictable, 44% of subjects were non-production staff, whereas the study population in the study of Venables *et al* were all production staff and included a higher percentage of smokers and some atopic subjects.

All PSS sensitive subjects developed symptoms and signs of allergic disease but this was subsequent to positive skin prick in most cases, the median interval being 8·5 months. Positive response to platinum salt skin prick test thus had a 100% positive predictive value for symptoms and signs of PSS (if exposure continued). Prompt, permanent removal from exposure at positive skin prick test may well avoid subsequent progression of the disease process.[12] Bias in diagnosis resulting from previous knowledge of skin prick results was a possibility, but was probably minimised by the refinery medical officer's experience in cases of PSS.

Subjects who were PSS symptomatic were investigated as they made up almost a third of the workers lost to employment for medical reasons in this study. Other researchers have identified similar cases,[12] but exact aetiology has not been established. This group probably comprises subjects reacting by more than one mechanism. Studies have identified subjects who develop symptoms and signs before a positive skin prick response[10 16]; and symptomatic workers who reacted to platinum salts on bronchial provocation testing, despite non-response to skin prick tests.[9] Some symptoms and signs may be related to other allergens and irritants used in the refining process, or to smoking (smokers in this group were all heavy smokers).

An association between disease related to platinum salts and smoking has been noted in other studies. Venables *et al*[10] showed smoking to be the most important predictor of sensitisation with risk estimated as four to five times greater in smokers than in non-smokers. Our higher (eightfold) risk estimate in smokers may be explained by differences in the rate of staff turnover. Within 24 months the decline in the population in the study of Venables *et al* was 30% higher than in ours, and smokers were more likely to leave (as in our study), so relatively more potential candidates for sensitisation, particularly smokers, were lost to the other study. Consistent with findings of this study a dose-response effect between cigarettes smoked a day was not found in PSS sensitive cases, but was evident among PSS symptomatic subjects who smoked.

Smoking and increased intensity of exposure were shown to be independently strongly associated in PSS sensitive cases: we were unable to confirm an interaction between the factors (suggested in fig 2) with interactive terms (smoking × exposure) possibly due to the relatively small data set.

Reservations expressed about bias exerted by "survivor" populations on cross sectional surveys were confirmed by this study. Within 24 months the study population of 78 was reduced by the ending of employment on medical grounds and natural attrition to 23. Non-smokers with low exposure accounted for 21% of entrants but 39% of the survivors, and smokers with high exposure were 32% of entrants but only 4% of the survivor group. Examination of the study by Venables *et al*[10] indicates a similar pattern. If this occurs in other refineries it would contribute to the generally accepted understanding that most platinum salt sensitisation occurs within two years of employment; after this time most workers at greatest risk would have left the industry.

Logical recommendations would be employment of non-smokers, and continued reduction in concentration of platinum salts in the air of work areas. These measures, combined with prompt removal from exposure of all workers with a positive skin prick test to platinum salts should considerably reduce the incidence of sensitivity to platinum salt in refinery personnel.

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