Allergy to complex platinum salts: a historical prospective cohort study

Michel Niezborala, Robert Garnier

Abstract
Objective—To assess the incidence of allergy to complex platinum salts in a platinum refinery.
Methods—A historical prospective cohort study was carried out on 77 workers (67 men) who started work between 1 January 1979 and 31 December 1991 and who were not atopic on skin prick tests to three common allergens at the time of recruitment. Skin prick tests with complex platinum salts were carried out and diagnosis of allergy to complex platinum salts made by the company’s doctor. Skin tests and medical examinations were carried out routinely every six months. Follow up was until 30 September 1992 or until leaving refinery work.
Results—18 workers developed a positive result on skin tests and 23 developed symptoms, including all 18 subjects with positive skin tests; the probability of surviving (95% confidence interval (95% CI)) for 72 months after joining the company, with negative skin test results was 0.67 (0.51–0.79) or with no symptoms was 0.63 (0.49–0.75). The incidence of positive skin tests and symptoms was highest during the first two years of work. Symptoms occurred more frequently in September and October than during the other months of the year. The exclusion of atopic subjects did not seem to have resulted in a lower incidence of sensitisation. Smoking was a significant predictive factor for both positive skin tests (estimated relative risk 5·53) and symptoms (4·70).
Conclusion—The findings confirm that smoking is and that atopy may not be a high risk factor for the development of allergy to complex platinum salts. The high incidence of sensitisation and the available data on the clinical course of sensitised workers show that sensitised workers must be promptly and completely removed from exposure.

Keywords: platinum; allergy; incidence

In 1911, Karasek and Karasek were the first to report cases of allergy to complex platinum salts in humans. Since then, many authors have reported a high prevalence of sensitisation or allergy to complex platinum salts among refinery workers. However, little is known about the incidence of allergy to complex platinum salts. In 1978, Ruff et al. estimated that each year, 5% to 10% of the exposed workers in the company we studied became allergic to complex platinum salts; but the only previous longitudinal study which allowed estimation of incidence of allergy to complex platinum salts was that of Venables et al. In that study, the incidence was of 3·1% person-months in the first two years of follow up and of 2·4% person-months in the total follow up period (between six and seven years).

A preliminary study of that cohort showed an increased incidence of occupational allergy in atopic workers but did not examine smoking. Since then, Hughes recommended that atopic workers should be excluded from refinery work. This was possible because of the introduction of skin prick tests with three common environmental allergens (house dust, house dust mite, and mixed grass pollens) into the pre-employment medical examination as an objective test for atopy. From 1979, Hughes’ medical surveillance programme was adopted in the company we studied (see methods); but several recent studies questioned this programme. Venables et al. showed that the risk from atopy was smaller than that for smoking and was not significant after taking account of smoking in a proportional hazards regression model. Moreover, three cross-sectional studies did not show any significant link between atopy and allergy to complex platinum salts and Baker et al. showed that allergy to complex platinum salts was strongly associated with cigarette smoking.

Therefore, the objectives of our study were:—to describe the incidence of allergy to complex platinum salts among exposed workers hired since 1979 in the company under study;—to compare this incidence with that estimated in 1978 by Ruff et al;—to confirm the predictive role of smoking in the onset of allergy.

Moreover, our personal findings led us to think that workers were more likely to develop symptoms when re-exposed to platinum salts after an interruption during their holiday and that the younger workers were more often sensitised than other workers. In this study, we also intended to confirm these hypotheses.

Materials and methods
Medical records were reviewed of 77 workers, hired between 1 January 1979 and 31
December 1991, who were non-atopic on skin prick tests to three common allergens. These workers were exposed to complex platinum salts and were examined medically at least twice. Out of these 77 all but one had undergone skin prick tests with complex platinum salts at least once.

The medical surveillance programme included pre-employment selection and surveillance during employment.

The pre-employment selection was: an interview to record sex, age, geographical origin, position to be occupied, any personal or family allergic history, the smoking status was recorded sporadically until 1986 and systematically since then; a physical examination, and since 1979 a search for any atopy according to Hughes' recommendations.14 Atopy was defined as one or more weals of at least 3 mm in diameter on skin prick tests with mixed grass pollen, house dust, and house dust mite (Parteur). Prick tests were made by introducing the tip of separate small hypodermic needles at a low angle into the epidermis of the forearm with a gentle lifting motion through drops of the test solutions on the skin. Reactions were read after 10 minutes. No control tests were used. Atopic subjects were not hired.

During employment the surveillance was a medical examination and skin prick tests to complex platinum salts carried out by the company's doctor on all exposed workers every six months. Routine screening was performed according to the method of Cleare et al16 with freshly prepared solutions of ammonium hexachloroplatinate and potassium tetrachloroplatinate both at concentrations of 1 g/l. Indeed, Cleare et al16 found that a 1 g/l concentration gave negative reactions in all non-exposed, non-sensitive subjects. A positive test result was defined as one or two weals of at least 3 mm in diameter. No control tests were used. The date of first positive test result or, in the absence of a positive result, of the last negative test result was noted.

The medical records were reviewed for the development of symptoms. These were defined as a diagnosis of allergy to complex platinum salts made by the company's doctor (asthma, rhinitis, urticaria, eczema). Diagnosis was based on two criteria: a history suggestive of occupational allergy (in particular, an improvement of symptoms during weekends and holidays) and the result of skin tests if available.

The data from the medical records were used to find the occupational and medical outcome of those workers who had become allergic to complex platinum salts, any transfers to different work stations, as well as the course of their symptoms and treatments.

The workers were followed up until 30 September 1992 or until leaving their position at the refinery, whichever was earlier. Leaving the position at the refinery was defined as either quitting the company or being transferred to a different position within the company.

The outcome of the sample was described by survival curves established with the Kaplan-Meier method for both skin tests and symptoms. Survival was defined as persistence of a negative skin test or the absence of symptoms of allergy to complex platinum salts (see figs 1 and 2). The 95% confidence intervals (95% CIs) of the survival probabilities were calculated with the Greenwood variance according to the Rothman method. The proportional hazards regression model was used to identify factors when a man joined the company that predicted subsequent symptoms or a positive skin test (smoking and age). The possible part played by re-exposure after temporary absence from work in triggering the allergy was studied by comparing the number of cases which started after the holiday period, in September or October, with the theoretical percentage of 2/11 (two out of 11 working months).

Results
Between 1986 and 1991, 226 applicants for an exposed job were screened. Eighty two (36%) of these were non-atopic on skin prick tests to three common allergens. These workers were exposed to complex platinum salts and were examined medically at least twice. Out of these 77 all but one had undergone skin prick tests with complex platinum salts at least once.

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Table 1  Characteristics of the cohort when joining the company

<table>
<thead>
<tr>
<th>Subjects</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ratio men:women</td>
<td>67:10</td>
</tr>
<tr>
<td>Age (y)</td>
<td></td>
</tr>
<tr>
<td>15-24</td>
<td>39 (51)</td>
</tr>
<tr>
<td>25-34</td>
<td>26 (34)</td>
</tr>
<tr>
<td>35-44</td>
<td>8 (10)</td>
</tr>
<tr>
<td>45-54</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Smoker *</td>
<td>32 (42)</td>
</tr>
</tbody>
</table>

*Information not available on smoking for 11 subjects.

Table 2  Incidence of symptoms and of positive results to skin tests with complex platinum salts in refinery workers

<table>
<thead>
<tr>
<th>Follow up period (months)</th>
<th>≤ 3</th>
<th>3-6</th>
<th>6-12</th>
<th>12-24</th>
<th>24-48</th>
<th>&gt; 48*</th>
<th>Total*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive skin test result: Workers at start of period (n)†</td>
<td>76</td>
<td>73</td>
<td>65</td>
<td>50</td>
<td>37</td>
<td>26</td>
<td>76</td>
</tr>
<tr>
<td>Duration of period (person-months)‡</td>
<td>226-3</td>
<td>211-6</td>
<td>337-4</td>
<td>517-6</td>
<td>775-0</td>
<td>1009-8</td>
<td>3057-7</td>
</tr>
<tr>
<td>Cases in period (n)</td>
<td>0</td>
<td>5</td>
<td>6</td>
<td>5</td>
<td>0</td>
<td>2</td>
<td>18</td>
</tr>
<tr>
<td>Incidence (%)</td>
<td>0</td>
<td>2-36</td>
<td>1-78</td>
<td>0-97</td>
<td>0-97</td>
<td>0-2</td>
<td>0-59</td>
</tr>
<tr>
<td>Symptoms: Workers at start of period (n)†</td>
<td>77</td>
<td>73</td>
<td>64</td>
<td>51</td>
<td>36</td>
<td>27</td>
<td>77</td>
</tr>
<tr>
<td>Duration of period (person-months)‡</td>
<td>229</td>
<td>209</td>
<td>350</td>
<td>526</td>
<td>774</td>
<td>1043</td>
<td>3131</td>
</tr>
<tr>
<td>Cases in period (n)</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>5</td>
<td>0</td>
<td>13</td>
<td>23</td>
</tr>
<tr>
<td>Incidence (%)</td>
<td>1-75</td>
<td>2-39</td>
<td>1-71</td>
<td>0-95</td>
<td>0-13</td>
<td>0-19</td>
<td>0-73</td>
</tr>
</tbody>
</table>

*Up to 30 September 1992.
†At start of period, workers with a negative skin test result or without symptoms and still exposed to the risk.
‡Sum of exposure duration (in months) of each subject in period.
were atopic. Atopic men were not hired.

During the total period of follow up, 96 non-atopic workers joined the company and were exposed to complex platinum salts. Only 77 were medically examined at least twice. Most of the 77 workers were young men and 42% of them were smokers (table 1).

About two thirds of the workers have been followed up for at least one year and one third have been followed up for at least four years (range 2 months–12 years).

The company’s doctor diagnosed 23 cases of allergy to complex platinum salts: three cases of asthma, six cases of asthma with rhinitis, one case of asthma and urticaria, six cases of rhinitis, three cases of rhinitis and urticaria, one case of urticaria, and three cases of eczema. Eighteen of these 23 subjects had a positive skin test. Four of the other five workers had left the company before confirmation of the diagnosis and one remained negative to skin tests. For this man the diagnosis is almost certain because after he left the refinery he was once accidentally re-exposed to complex platinum salts and he immediately had asthma. All subjects with a positive skin test already had or subsequently developed symptoms. In 10 out of 18 cases, the symptoms occurred before the positive skin test.

The incidence of symptoms and positive skin tests with platinum salts was highest during the first two years of employment (table 2). Table 3 shows the probabilities of not developing any symptoms or of remaining negative to skin tests at different times during the follow-up period.

The smoking habits were recorded for 66 of the 76 workers who underwent at least one skin test. Three employees, out of the 10 with unknown smoking habits, developed a positive result to skin tests. Twenty out of 34 smokers less than 25 years old (58-8%) and 12 out of 32 workers 25 years old or more (37-5%) were smokers. Proportional hazards regression analysis showed that smoking was an important predictor of both symptoms and positive skin test result. When age at joining the company (< 25 years vs >= 25 years) and smoking were considered together in the model, the risk in smokers was 3.97 times (symptoms) and 4.90 times (skin tests) that in non-smokers (table 4). When considered alone in the model, age at joining the company was a significant predictor of both symptoms and a positive skin test result (the risk decreased with age); but when considered together with smoking in the model, age at joining the company was not a significant predictor (table 4).

In nine cases out of 23, the symptoms appeared in September or October. Comparison of this rate with the theoretical rate for a two month period (out of the 11 working months) showed a significant difference (P < 0.01). Thus, the symptoms appeared more frequently in September and October than during the other months of the year.

Five of the 23 workers with one or more symptoms were lost to follow up and the remaining 18 were declared unable to be further exposed to complex platinum salts by the

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**Table 3** Probability of survival with negative skin test result or with no symptoms in refinery work

<table>
<thead>
<tr>
<th>Follow up date (months)</th>
<th>6</th>
<th>12</th>
<th>24</th>
<th>72</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative skin test result:</td>
<td>Probability of survival (95% CI)</td>
<td>0.93 (0.85 to 0.97)</td>
<td>0.84 (0.73 to 0.91)</td>
<td>0.75 (0.62 to 0.84)</td>
</tr>
<tr>
<td>No symptoms:</td>
<td>Probability of survival (95% CI)</td>
<td>0.90 (0.81 to 0.95)</td>
<td>0.81 (0.71 to 0.88)</td>
<td>0.72 (0.60 to 0.81)</td>
</tr>
</tbody>
</table>

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**Table 4** Summary of proportional hazards regression analysis to identify factors at joining the company that predicted subsequent symptoms or a positive skin test result to complex platinum salts in refinery workers

<table>
<thead>
<tr>
<th>Outcome skin test result:</th>
<th>Workers n</th>
<th>Risk estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive smoke test result:</td>
<td>66</td>
<td>5.53 (1.56 to 19.72)</td>
</tr>
<tr>
<td>Age &lt; 25 v age &gt;= 25</td>
<td>66</td>
<td>3.17 (1.12 to 8.94)</td>
</tr>
<tr>
<td>Smoker v non smoker</td>
<td>66</td>
<td>4.90 (1.35 to 17.82)</td>
</tr>
<tr>
<td>Age &lt; 25 v age &gt;= 25</td>
<td>66</td>
<td>1.74 (0.58 to 5.23)</td>
</tr>
<tr>
<td>Symptoms:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoker v non smoker</td>
<td>66</td>
<td>4.70 (1.54 to 14.31)</td>
</tr>
<tr>
<td>Age &lt; 25 v age &gt;= 25</td>
<td>77</td>
<td>4.09 (1.52 to 11.09)</td>
</tr>
<tr>
<td>Smoker v non smoker</td>
<td>66</td>
<td>3.97 (1.28 to 12.27)</td>
</tr>
<tr>
<td>Age &lt; 25 v age &gt;= 25</td>
<td>66</td>
<td>2.36 (0.83 to 6.74)</td>
</tr>
</tbody>
</table>

*Considered alone in model; †Smoking and age considered together in model.
company physician. The median interval between the appearance of the symptoms and the physician's decision was 3-5 months (range 0-30 months). The median interval between the date of the first positive skin test and the physician's decision was 5-5 months (range 0-22 months). The occupational outcome was known for 16 out of 18 workers and the medical outcome for 12 out of 18 workers. Nine continued to work in the same building as the refining workshop. The symptoms disappeared in only one of them. Three were transferred to a different zone; the symptoms disappeared in two and the third still had a non-specific airway hyperreactivity. This worker, who was transferred later because of a persistently negative skin test showed a clinical improvement of his asthma, but was still sensitive to irritating substances and at the time of the report had to undergo episodic treatments.

Discussion
Our study was conducted on data which were not collected for the purpose of the study. Some problems result from this.

The skin prick tests were made without control tests. This could have resulted in imprecision. However, the frequency of atopy in the pre-employment screening was 36%; this result is very similar to that reported in other studies. Furthermore, we noted that in eight cases out of 18, the positive result to skin prick test with complex platinum salts preceded the symptoms and all these workers subsequently developed symptoms; thus no false positive results were found in these cases.

The smoking histories were incomplete. This point is discussed later.

The level of exposure to the complex platinum salts of the workers was not known. The published data show that the risk of developing an allergy to the complex platinum salts is correlated with the intensity of exposure. Could the lack of data on the exposures result in a bias when studying the relation between smoking or the age at joining the company and the occurrence of sensitisation? We think it is unlikely because the existence of a link between smoking or the age at joining the company and the level of exposure seems very improbable and thus the level of exposure is probably not a confounding factor.

Some diagnoses of allergy to complex platinum salts recorded in the medical notes are questionable. The symptoms of allergy to complex platinum salts are not specific even if the history is suggestive of occupational allergy because the workers exposed to platinum salts are also exposed to many other irritating or sensitising chemicals. Yet, the diagnosis was based only on medical history, and thus is doubtful, in four workers. A fifth worker had a persistent negative skin test to the complex platinum salts but his diagnosis is definite because he had asthma after accidental re-exposure to platinum salts. The positive skin test to complex platinum salts, which is highly specific, was positive in the other 18 workers. In these workers the diagnosis of sensitisation to complex platinum salts seems definite even if the relation between the positive skin test result and the onset of an eczema in three workers is questionable.

In our cohort, the incidence of a positive, skin test was 0-59% person-months and the incidence of a diagnosis of allergy to complex platinum salts made by the company doctor was 0-73% person-months. These estimated rates probably underestimate the true rates, because some sensitised workers could have left the company before the company doctor could make a diagnosis (96 workers joined the company and were exposed to complex platinum salts, but only 77 were medically examined at least twice). Be that as it may, the incidences are very high and an improvement in the prevention of this risk seems to be absolutely necessary.

In our study, the incidence of symptoms and positive results to skin tests were strongly related to the period since the start of employment. The symptoms appeared during the first two years in 20 out of 23 subjects whose positive skin test was found in 16 out of 18. These results confirm the findings of Venables et al. The risk of developing an allergy to platinum salts occurs mainly during the first two years of employment. The incidence of sensitisation in the cohort of Venables et al. was higher at each follow up period than in ours except after 48 months. All the subjects included in their cohort were chemical process operators in the platinum group metal refineries and therefore were probably highly exposed to complex platinum salts. In our cohort, all exposed workers were included, but some of them were only occasionally exposed. This would explain the difference of incidence between the two cohorts.

In 1979, Ruff et al. reported that, each year in the company which we studied, 5% to 10% of exposed workers became allergic to complex platinum salts and needed to be transferred to a different workplace. Our results showed an incidence of 0-73% person-months (8-8% person-years) and after 1979 the conditions of exposure were similar to those before 1979. Indeed, no special industrial hygiene measures were undertaken to eliminate exposure to platinum salts in this period. Thus, to screen atopic subjects with common allergens when they joined the company did not seem to result in a reduction of the incidence of allergy to complex platinum salts. This finding is in agreement with four recent studies which did not show any significant link between atopy and allergy to complex platinum salts. It is important to stress that in our company, before 1979 people with a history of lung disease, asthma, or allergy were not exposed to complex platinum salts. This could explain why the new measures of identification and exclusion of atopic subjects did not have the expected efficacy. Moreover, in our screening protocol we used only two types of allergens (house dust and house dust mite are virtually the same) so that some atopic men may have been missed.

In our cohort, the risk of developing a positive result to skin tests in smokers was 5-53
times that in non-smokers. Despite the difference of incidence of sensitisation between the two cohorts, this result is similar to that of Venables et al.14 who found a relative risk of 5.05 when adjusting for atopy. However, the validity of our results needs to be confirmed. Indeed, in our cohort, the smoking habits of 10 workers were not identified. The missing data could result in a bias. This hypothesis seems unlikely as the missing data were related to the fact that the first of the three doctors working for the company between 1979 and 1992 did not systematically record the smoking habits of the workers. The two other doctors systematically registered the smoking habits of workers, even before suspecting the part played by tobacco in the development of sensitisation. Thus, the missing data do not seem to be related to either exposure or to the disease. Tobacco can therefore be considered to be an important risk factor of sensitisation in our study as Venables et al.12 and Baker et al.13 have studied the part played by tobacco among 107 current employees of a platinum refinery. Fourteen workers, out of the 68 current or past smokers, had a positive result to skin tests v one out of 38 non-smokers; this corresponds to an odds ratio of 9.0 after adjustment for aeroallergen skin test status. The results of Baker et al.12 and our own results support the hypothesis of a relation between smoking and the development of allergy to complex platinum salts as described by Venables et al.13

Age at joining the company was a significant predictor of both symptoms and a positive skin test when considered alone in the model but a non-significant predictor when considered together with smoking in the model. Two reasons could explain this finding:

—The proportion of smokers was higher in the younger group.
—When age was considered alone, the model included 77 subjects, but when age was considered together with smoking, the model included only the 66 subjects in whom smoking habits was defined. Thus, the statistical power of this test was weaker than that of the first test.

Symptoms occurred more frequently in September and October than during the other months of the year. In this company, workers generally went on holiday in August and sometimes in September. The period corresponding with the return from holiday could be a convenient marker of the onset of progressive symptoms. Indeed, this is an easy chronological reference and workers could at this time be more easily aware of the pathological nature of their symptoms due to the improvement during their holiday and to the recurrence when resuming work. Furthermore, an increased incidence of symptoms in spring raises the idea that some other cause such as hay fever resulting from the pollens in spring may be responsible for some of the symptoms attributed to complex platinum salts. However, exposure after an interruption could favour the development of clinical signs of allergy to complex platinum salts. This finding should be confirmed in other studies.

The occupational and medical outcome of workers was not complete. However, most of them remained in the zone of the refining workshop and almost all of them continued to have more or less disabling allergies as found by Hughes.14 These workers were probably so exquisitely sensitive to small amounts of complex platinum salts that work related symptoms persisted. Indeed, Baker et al.13 have shown, by atmospheric measures, that platinum salts are present near the production zones. It could be difficult to conclude that there are after effects as most workers remained exposed to platinum salts and therefore remained symptomatic. On the other hand, one subject who was removed from the risk area quite late, and who was not exposed to the risk thereafter, retained a non-specific bronchial hyperreactivity requiring him to occasionally take medications. This isolated finding confirms those made by Baker et al.10 among 29 former employees who had to end their employment due to respiratory symptoms. As we have done, Baker et al.13 questioned the delay between the development of hypersensitivity and the removal from the risk area. It is therefore important to remove sensitised subjects from the risk as quickly as possible. This removal should take place as soon as a worker becomes positive to a skin prick test with complex platinum salts even if he does not yet show any symptoms, as, like Venables et al.12 we have found that subjects with a positive skin test already had or subsequently developed symptoms.

Conclusion

Despite the medical surveillance programme for platinum refinery workers, the incidence of allergy to complex platinum salts remains very high. Thus, we recommend that the risk should be reduced as much as possible. At no stage should a worker be able to come into contact with a solution or a solid containing these particular complex platinum salts.

People with a positive skin prick test, to one or more of the three common allergens but without a history of lung disease, asthma, or allergy, should not be excluded from exposure to complex platinum salts.

Encouragement should be given to the workers to stop tobacco smoking.

People with a positive skin test to platinum salts but without symptoms should be removed from exposure.

All people who are diagnosed to have an allergy to complex platinum salts should be advised to leave the factory site.

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Allergy to complex platinum salts: a historical prospective cohort study


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