

Exposure-effect relationship of platinum salt allergy in a catalyst production plant: Conclusions from a 5-year prospective cohort study

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Background: There is a high incidence of occupational asthma and rhinitis caused by platinum (Pt) salts in precious-metal refineries.

Objective: We sought to assess exposure to Pt salts and the incidence of Pt salt allergy in a catalyst production plant.

Methods: A 5-year prospective cohort study was performed in 159 catalyst production workers (94.6% of recruited), 50 craftsmen (92.6% of recruited), and 66 control subjects (76.7% of recruited) at yearly intervals. Subjects were assigned to exposure categories of high levels of Pt ($n = 115$), persistently low levels of Pt ($n = 51$), intermittently low levels of Pt ($n = 61$), or no Pt ($n = 48$) after the initial survey according to job title and job location. Skin prick test conversion from a negative response to a 4 mm or larger wheal response with a 10^{-2} mol/L hexachloroplatinic acid solution was chosen as the outcome variable.

Results: Exposure assessment of airborne Pt and Pt in the serum of workers demonstrated clear differences between exposure categories. The threshold limit value of $2 \mu\text{g}/\text{m}^3$ for soluble Pt was exceeded in 3 (4%) of 78 measurements. Thirteen subjects assigned to high exposure showed skin test conversion, and new allergic symptoms were associated with exposure. Among the high-exposure category, the incidence rate of skin prick test conversion was 5.9 per 100 person-years for newly employed subjects ($n = 79$) and 2.1 per 100 person-years for those who had already been employed at the time of the initial survey ($n = 36$). A predicting factor for skin test conversion in highly exposed subjects was smoking status (relative

risk, 3.9; 95% confidence interval, 1.6-9.7) but not atopy or bronchial hyperresponsiveness.

Conclusion: Sensitization to Pt salts may develop in workers of catalyst production plants. Both the exposure to Pt salts and the incidence of Pt salt allergy were lower compared with reported data from precious-metal refineries. (*J Allergy Clin Immunol* 2000;105:364-70.)

Key words: Platinum, exposure, allergy, catalyst, sensitization, occupational, asthma, rhinitis, risk assessment

Platinum (Pt) salts are highly potent occupational allergens causing asthma, rhinitis, conjunctivitis, and contact urticaria in a high percentage of workers of precious-metal refineries. Exposure assessment in refineries in the United States and South Africa was reported to frequently exceed the limit of $2 \mu\text{g}/\text{m}^3$.^{1,2} Pt salts are increasingly used in catalyst production, but (with the exception of one Russian study³) data about exposure and Pt salt-induced asthma in these plants have not been reported. Because of more uniform production processes and intensified protective measures, lower Pt salt exposures and a lower incidence of Pt salt allergy may be expected in catalyst production plants. It was the aim of this study to assess both the exposure to Pt and the incidence of sensitization to Pt salt in a catalyst production plant in a 5-year prospective cohort study and to possibly define a threshold value for sensitization.

METHODS

Description of the catalyst production process

The Pt salt solution is prepared in a closed system and is then brought to an impregnation area, where different substrates are immersed in the Pt salt solution by robots. The impregnation area is encapsulated and separately ventilated. Access to this area is only allowed with specific protective clothing, including gloves and airstream breathing devices. However, workers often enter the impregnation areas without personal protection equipment during sudden malfunctions. Finally, the catalysts undergo a reduction process in a furnace.

Subjects and grouping

All catalyst production employees ($n = 65$); newly employed catalyst workers during the study period ($n = 103$); craftsmen with fre-

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TABLE I. Recruitment and study cohorts

	Employed before the study	Employed during the study	Total
Catalyst workers			
Recruited	65	103	168
Refused study	6 (9.2%)	4 (3.9%)	10 (6.0%)
Left study	8 (12.3%)	15 (14.6%)	23 (13.7%)
Positive SPT response, initial survey	4 (3.9%)	0	4 (2.4%)
Remained in study	51 (78.5%)	80 (77.7%)	131 (78.0%)
At least 2 examinations	63 (96.9%)	96 (93.2%)	159 (94.6%)
Craftsmen			
Recruited	37	17	54
Refused study	8 (21.6%)	3 (17.6%)	11 (20.4%)
Left study	6 (16.2%)	3 (17.6%)	9 (16.7%)
Positive SPT response, initial survey	0	0	0
Remained in study	23 (62.2%)	11 (64.7%)	34 (63.0%)
At least 2 examinations	34 (91.9%)	16 (94.1%)	50 (92.6%)
Control subjects			
Recruited	64	22	86
Refused study	23 (35.9%)	7 (31.8%)	30 (34.9%)
Left study	9 (14.1%)	6 (27.3%)	15 (17.5%)
Positive SPT response, initial survey	0	0	0
Remained in study	32 (50.0%)	9 (40.9%)	41 (47.7%)
At least 2 examinations	50 (78.1%)	16 (72.7%)	66 (76.7%)
Total			
Recruited	166	142	308
Refused study	37 (22.3%)	14 (9.9%)	51 (16.6%)
Left study	23 (13.9%)	24 (16.9%)	47 (15.3%)
Positive SPT response, initial survey	4 (2.4%)	0	4 (1.3%)
Remained in study	106 (63.9%)	100 (70.4%)	206 (66.9%)
At least 2 examinations	147 (88.6%)	128 (90.1%)	275 (89.3%)

Remained in study means that these workers were available during the last examination; that is, they had not been transferred, had not refused, and had not left the study for any reason. Note that some subjects refused or left after 2 or more examinations. Thus the number of those with more than one examination, those who refused, and those who left do not represent the number of recruited subjects. Subjects with at least 2 examinations represent the study population.

Abbreviations used

EAST: Enzyme allergosorbent test
Pt: Platinum
SPT: Skin prick test

quent jobs in the catalyst department ($n = 37$); newly employed craftsmen ($n = 17$); control subjects from the canteen, administration, and security staff of the plant ($n = 64$); and newly employed blue collar workers of other departments ($n = 22$) took part in a prospective cohort study between December 1989 and July 1995 (Table I). Fifty-one (16.6%) subjects did not allow tests often after they had performed 2 or more surveys. Forty-seven (15.3%) subjects left the plant before the end of the study. Subjects with at least one follow-up examination ($n = 275$) were included in the statistical analysis. This represents a total of 94.6% of the catalyst department, 92.6% of the craftsmen, and 76.7% of the control subjects. No pre-employment selection had been performed. If subjects changed jobs or were transferred for organizational reasons, only the periods spent in the high-exposure area were considered. If a catalyst worker was transferred to other departments, he was examined once after the transferral and excluded afterward. Because there was an intensive change of job locations among catalyst operators, a clear assignment caused by Pt measurements was not considered. Instead, subjects were assigned after the initial survey to one of 4 categories according to job title and job location. Subjects working directly in production lines were included in the high-exposure category. This was a rather uniform group because opera-

tors worked in all production lines and in all parts of the lines. The high-exposure category also contained craftsmen engaged in maintenance or demolition of production lines. The category with persistently low exposure consisted of people working within the catalyst department but not in the production lines (ie, white collar employees or workers of the wash coat preparation, quality control, analytic laboratory, or warehouse staff). Subjects who entered the catalyst building intermittently, among them 19 subjects originally recruited as control subjects (eg, craftsmen who never worked in the production lines or security staff), were assigned to the intermittent low-exposure category. This category was obviously exposed to a considerably lower degree than the persistently low-exposure subjects. Subjects who never entered the catalyst building were assigned to the no-exposure category. Almost all craftsmen were either considered highly exposed (production line maintenance) or intermittently exposed to low levels (tasks outside the lines). The study was accepted by the ethics committee of the university.

Protocol

Examinations were performed in the medical department of the plant (Degussa, Rheinfelden). Subjects were examined in intervals of 6 months during the first year and afterward in yearly intervals. If a subject was not available because of vacation or illness, the examination was conducted 6 months later. Personal data, as well as symptoms, were obtained by a questionnaire. If the subject reported any symptom, more detailed information was obtained by the author throughout the study. Smoking of cigarettes, but not cigars or pipes, was considered. Previous jobs, as well as current occupational exposure time, job title, and job location, were recorded.

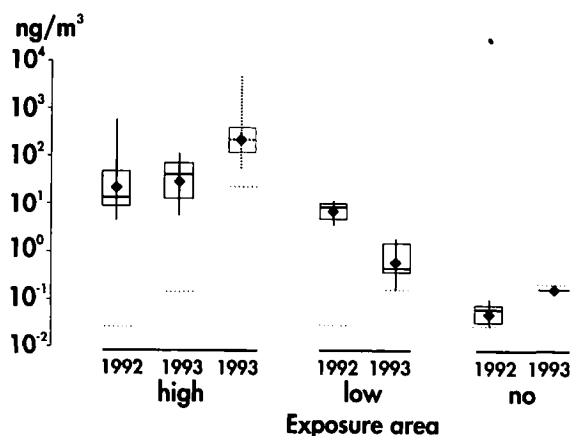


FIG 1. Soluble Pt in exposure areas. The box-and-whisker plots represent medians, lower and upper quartiles, and minimal and maximal values. Dots represent geometric means. The dotted plot represents personal sampling (performed in 1993 only), and the dotted lines represent the detection limits. The number of measurements are (from the left) 16, 12, 22, 8, 8, 8, and 4.

The work relation of symptoms was recorded, and their onset was assigned to (1) before joining the plant, (2) after joining the plant but before the study, and (3) during the study. Asthma was defined as variable wheeze, shortness of breath, or both. Rhinitis was defined as recurrent runny nose, sneezing, or both without obvious common cold. Conjunctivitis was defined as itching or burning eyes. Dermatitis was defined as recurrent affection of the skin without obvious other diagnoses (eg, psoriasis). Symptoms reported as nonrecurrent were not considered.

Skin prick test

Skin prick tests (SPTs) were performed with cat dander, grass and birch pollen, *Dermatophagoides pteronyssinus*, and *Alternaria alternata* (Allergopharma, Reinbek, Germany). SPT with Pt salts were performed with hexachloroplatinic acid 10^{-2} mol/L (4.1 g/L) diluted in 0.9% NaCl from a 10^{-1} mol/L stock solution (provided by Degussa). A wheal diameter of 4 mm or larger than that produced by the negative control was considered positive. Atopy was defined as a positive reaction to one or more environmental allergens.

Lung function

FEV₁ was measured with a pneumotachograph (CustoVit; Customed, Munich, Germany). Reference values were chosen as described recently.⁴

Bronchial hyperresponsiveness

Bronchial responsiveness to histamine (Merck, Darmstadt, Germany) was assessed, as described recently.⁵ A provocative dose causing a 15% decrease in FEV₁ of 1 mg was used as the threshold for bronchial hyperresponsiveness. Responsiveness was also expressed by the slope of a line extending from the origin of the dose-response curve to the last data point.⁶ Forty-nine tests (47 subjects [8.9%]) were not performed or not allowed.

Total serum IgE and enzyme allergosorbent test

Total IgE was measured with Phadezym PRIST, and specific IgE to environmental allergens was measured with Phadezym RAST (Pharmacia, Freiburg, Germany). The same allergens as in the skin tests were used. An enzyme allergosorbent test result of class I or greater was considered positive.

Pt air concentrations

Airborne Pt concentrations were measured in 1992 and 1993. Measurements were performed with a modified standard method for the detection of Pt, which defines soluble Pt by the amount of Pt that is dissolved in 0.07 mol/L hydrochloric acid.⁷ Area sampling was carried out with a high-volume collector (Gravicon VC25; Stroehlein, Kaarst, Germany). The dust was collected on glass fiber filters with a diameter of 150 mm (Sartorius, Goettingen, Germany). The sampling periods varied between 12 and 17 hours. Because of different analytic procedures, the detection limits were about 0.025 ng/m³ in 1992 and 0.13 ng/m³ in 1993. Personal sampling was performed in 1993 in highly exposed subjects by using an Alpha 1 pump (Du Pont, Bad Homburg, Germany). The sampling periods lasted about 8 hours, and the detection limit was about 20 ng/m³.

Pt measurement accuracy was ascertained by using a quality control program instituted by the German Ministry of Education, Science, Research, and Technology. Analysis was performed by inductively coupled plasma emission spectrometry (PQ2+; Fisons Instruments, Mainz, Germany) or graphite furnace atomic absorption spectrometry (PE 4000 ZL and PE 4100ZL; Perkin-Elmer, Ueberlingen, Germany).

Pt serum concentrations

Sera of 50 subjects (10 catalyst operators, 30 subjects of the persistent low-exposure category, and 10 persons with no exposure) were chosen from the survey in January 1994. Measurements were performed by adsorptive voltammetry, as described recently.⁸ The detection limit was 0.2 ng/L.

Statistical analysis

Arithmetic or geometric means for skewed data with 95% confidence intervals are given. For calculations, values of IgE and the slopes of the histamine dose-response curves were log-transformed. Because SPTs with Pt salts have been reported to be highly specific and sufficiently sensitive,⁹ SPT response conversion from negative to positive was chosen as the primary outcome variable, but new symptoms (asthma, rhinitis, conjunctivitis, or dermatitis) were also used as dependent variables. Predicting factors for SPT conversion were determined by a multivariate analysis considering exposure category, age, atopy, smoking status, pre-existing symptoms of asthma, total IgE, FEV₁, and bronchial responsiveness to histamine at the initial survey, as well as employment before or during the study. Age-adjusted relative risks were calculated for the high-exposure category by using the logit method. Calculations were performed with SAS (SAS Institute Inc, Cary, NC). A *P* value of less than or equal to .05 was considered significant.

RESULTS

Exposure assessment

Measurements of airborne soluble Pt demonstrated 10- to 100-fold differences between medians of exposure areas. Personal sampling yielded higher Pt concentrations than area sampling (Fig 1). The current threshold limit value of 2 µg/m³ was exceeded in 3 (4%) of 78 measurements, all of which were obtained after personal sampling in highly exposed operators. There was a 1000-fold variability of the concentrations at the production lines. Measurements in low-exposure areas within the catalyst production were below 10 ng of soluble Pt per cubic meter (85 ng of total Pt per cubic meter). Soluble Pt in control areas outside the catalyst

TABLE II. Personal data according to exposure categories

	Exposure category			
	High (n = 115)	Persistent low (n = 51)	Intermittent low (n = 61)	No (n = 48)
Recruitment group				
Catalyst department	104 (90.4%)	51 (100%)	4 (6.6%)	0
Craftsmen	11 (9.6%)	0	38 (62.3%)	1 (2.1%)
Control subjects	0	0	19 (31.1%)	47 (97.9%)
Age (y)	32 (30-34)	32 (29-35)	39 (36-42)	38 (35-41)
Males	115 (100%)	48 (94.1%)	60 (98.4%)	41 (85.4%)
Smoking status*				
Smokers	53 (46.1%)	16 (31.4%)	18 (29.5%)	16 (33.3%)
Nonsmokers	24 (20.9%)	23 (45.1%)	24 (39.3%)	16 (33.3%)
Exsmokers	38 (33%)	12 (23.5%)	19 (31.1%)	16 (33.3%)
Pack-years	9 (7-11)	6 (4-8)	9 (6-12)	11 (7-15)
In plant before initial survey (mo)	31 (17-45)	72 (49-95)	144 (124-164)	123 (100-146)
OET before initial survey (mo)	21 (15-27)	43 (30-56)	91 (75-107)	—
Time between initial and final survey per subject (mo)	33 (29-37)	46 (40-52)	43 (38-48)	39 (33-45)
Surveys per subject	4.6 (4.2-5.0)	5.3 (4.8-5.8)	5.3 (4.8-5.8)	4.5 (4.0-5.0)

Values represent arithmetic means or geometric means of skewed data with 95% confidence intervals or percentages in parentheses. Note that 19 subjects originally recruited as control subjects were assigned to the intermittent low-exposure category (see the "Methods" section).

OET, Occupational exposure time.

*Smokers and exsmokers were taken as one group for calculations.

building was in the range of 30 to 90 pg/m³. Concentrations of total Pt were about 10-fold higher than concentrations of soluble Pt. The ratios of soluble and metallic Pt varied but were consistent with expected ratios according to the sampling location (data not shown). Pt concentrations in serum samples confirmed clear differences between the high-exposure category and both other categories (Fig 2).

Personal data and assessment of health effects

The number of smokers was somewhat higher in the high-exposure category. Because of the large number of newly employed subjects in the catalyst department, exposure periods, as well as study periods, were lower in the high-exposure category (Table II).

Atopy was equally frequent among categories both at the initial and final survey. Conversion of SPT with Pt salt occurred only in the highly exposed category (n = 13) with the exception of one subject initially grouped as having persistently low exposure. After SPT conversion, this worker admitted occasional higher contact when impregnating small series of catalysts by hand. Thus SPT conversion occurred only in subjects working directly at Pt salt sources. The incidence of SPT conversion was 4.1 per 100 person-years in the highly exposed category (n = 13 converters).

Among the high-exposure category, SPT conversion occurred in 10 newly employed operators and in 3 subjects (2 operators and 1 craftsman) who had already worked in the plant before the initial survey (for 68, 16, and 10 months). Nine of the 13 subjects converted during the third year of the follow-up, with the remainder converting during years 1, 2, 4, and 5 after their initial sur-

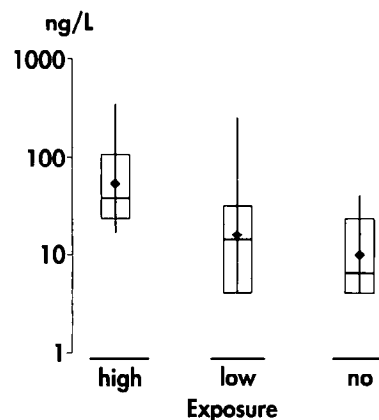


FIG 2. Pt concentrations in serum of employees during the initial survey according to exposure categories. The number of measurements are (from the left) 10, 30, and 10.

vey. An incidence rate of 5.9 per 100 person-years was calculated for newly employed subjects, and an incidence rate of 2.1 per 100 person-years was calculated for those who had already been employed at the time of the initial survey.

Further parameters did not differ between exposure categories (Table III). New symptoms beginning during the study, both with and without relation to work, were clearly more frequent in the high-exposure category (Tables IV and V). No subject with a negative SPT response and new work-related symptoms (n = 6) showed SPT conversion at follow-up examinations. All converters reported new symptoms during the study, but these were work related in only 9 of the 14 subjects (rhinitis, 43%; dermatitis, 36%; and asthma and conjunctivitis, 29%). If the subject that was misclassified was

TABLE III. Results of SPTs to environmental allergens and Pt salt, total IgE, FEV₁, and histamine testing according to exposure categories

	Exposure category			
	High (n = 115)	Persistent low (n = 51)	Intermittent low (n = 61)	No (n = 48)
Environmental allergens: positive SPT and EAST responses				
Initial survey				
Grasses	7 (6.1%)	7 (13.7%)	7 (11.5%)	4 (8.3%)
Birch	4 (3.5%)	1 (2.0%)	5 (8.2%)	3 (6.3%)
<i>Dermatophagoides pteronyssinus</i>	9 (7.8%)	3 (5.9%)	4 (6.6%)	7 (14.6%)
Cat dander	3 (2.6%)	0	3 (4.9%)	2 (4.2%)
<i>Alternaria alternata</i>	0	0	0	0
Any	19 (16.5%)	10 (19.6%)	13 (21.3%)	11 (22.9%)
Final survey				
Grasses	7 (6.1%)	9 (17.6%)	5 (8.2%)	3 (6.3%)
Birch	2 (1.7%)	3 (5.9%)	4 (6.6%)	3 (6.3%)
<i>Dermatophagoides pteronyssinus</i>	8 (7.0%)	4 (7.8%)	3 (4.9%)	6 (12.5%)
Cat dander	1 (0.9%)	0	2 (3.3%)	2 (4.2%)
<i>Alternaria alternata</i>	0	0	0	0
Any	15 (13.0%)	13 (25.5%)	12 (19.7%)	12 (25%)
Pt salt: positive SPT response				
Initial survey*	0	0	0	0
Final survey	13 (11.3%)	1 (2.0%)	0	0
Total IgE (kU/L)				
Initial survey	33 (30-80)	36 (31-108)	33 (29-66)	26 (23-66)
Final survey	37 (33-114)	31 (27-137)	40 (35-121)	34 (29-118)
FEV ₁ (% predicted)				
Initial survey	101 (99-103)	103 (100-106)	104 (100-108)	106 (102-110)
Final survey	100 (97-103)	103 (100-106)	102 (98-106)	103 (99-107)
FEV ₁ <90% predicted				
Initial survey	20 (17.4%)	7 (13.7%)	14 (23.0%)	4 (8.3%)
Final survey	22 (19.1%)	9 (17.7%)	13 (21.3%)	6 (12.5%)
Bronchial hyperresponsiveness tests				
not performed	16 (7%)	13 (13%)	11 (9%)	9 (9%)
Dose-response slope (%·mg ⁻¹)				
Initial survey	2.3 (2.1-4.2)	1.5 (1.3-3.4)	2.5 (2.2-4.8)	2.5 (2.2-4.9)
Final survey	2.3 (2.1-3.1)	1.4 (1.2-2.6)	2.1 (1.9-5.1)	2.1 (1.8-5.7)
PD ₁₅ <1 mg histamine				
Initial survey	8 (7.1%)	1 (2.1%)	6 (9.8%)	1 (2.1%)
Final survey	7 (6.9%)	1 (3.4%)	3 (6.0%)	0

Values are mean values with 95% confidence intervals or percentages in parentheses.

*Four subjects with a positive SPT response to Pt during the initial survey were excluded.

TABLE IV. Symptoms according to exposure categories

	Exposure category			
	High (n = 115)	Persistent low (n = 51)	Intermittent low (n = 61)	No (n = 48)
Symptom occurrence before exposure				
Any	19 (16.5%)	11 (21.6%)	14 (23.0%)	7 (14.6%)
Shortness of breath-wheeze	3 (2.6%)	1 (2.0%)	5 (8.2%)	0
Runny nose-sneezing	14 (12.2%)	11 (21.6%)	11 (18.0%)	6 (12.5%)
Itching-burning eyes	8 (7.0%)	5 (9.8%)	7 (11.5%)	3 (6.3%)
Dermatitis	3 (2.6%)	1 (2.0%)	0	2 (4.2%)

included in the high-exposure category, specificity of any new work-related symptom was 0.94, and sensitivity was 0.64 for highly exposed subjects (using SPT conversion as the gold standard).

The multivariate analysis showed a strong association between SPT conversion and exposure (Table VI). In

addition, less-pronounced associations were found with smoking, total IgE levels (positive associations), and FEV₁ (negative association). Both smoking and FEV₁ were associated with the occurrence of new symptoms ($P < .02$ for both parameters; data not shown). The age-adjusted relative risk in the high-exposure category

TABLE V. Symptoms according to relation to work

	Relation to work							
	High (n = 115)		Persistent low (n = 51)		Intermittent low (n = 61)		No (n = 48)	
	No	Yes	No	Yes	No	Yes	No	Yes
Symptom occurrence after exposure but before study								
Any	5 (4.3%)	5 (4.3%)	6 (11.7%)	2 (3.9%)	12 (19.7%)	1 (1.6%)	1 (2.1%)	0
Shortness of breath-wheeze	2 (1.7%)	0	1 (2.0%)	0	5 (8.2%)	0	0	0
Runny nose-sneezing	2 (1.7%)	2 (1.7%)	5 (9.8%)	0	3 (4.9%)	0	1 (2.1%)	0
Itching-burning eyes	0	0	5 (9.8%)	1 (2.0%)	3 (4.9%)	0	0	0
Dermatitis	2 (1.7%)	3 (2.6%)	4 (7.8%)	1 (2.0%)	1 (1.6%)	1 (1.6%)	0	0
Symptom occurrence during study								
Any	23 (20.0%)	15 (13.0%)	3 (5.9%)	3 (5.9%)	3 (4.9%)	0	1 (2.1%)	3 (6.3%)
Shortness of breath-wheeze	6 (5.2%)	5 (4.3%)	2 (3.9%)	1 (2.0%)	0	0	0	0
Runny nose-sneezing	12 (10.4%)	10 (8.7%)	0	1 (2.0%)	1 (1.6%)	0	0	0
Itching-burning eyes	3 (2.6%)	4 (3.5%)	1 (2.0%)	0	1 (1.6%)	0	1 (2.1%)	1 (2.1%)
Dermatitis	7 (6.1%)	9 (7.8%)	0	2 (3.9%)	1 (1.6%)	0	0	2 (4.2%)

TABLE VI. Multivariate analysis to assess predicting factors of SPT response conversion to Pt

Independent variables	Mean square error	F value	P value	Age-adjusted relative risk in high-exposure category
Exposure (4 groups)	0.174	3.77	.011	—
Age (y)	0.009	0.19	.660	—
Smoking status (smoker/exsmoker/nonsmoker)*	0.136	2.96	.054	3.9 (1.6-9.7)
FEV ₁ (% predicted)†	0.195	4.24	.041	1.0 (0.7-1.3)
Bronchial hyperresponsiveness (slope)‡	0.125	2.71	.101	1.1 (0.9-1.3)
Atopy (yes/no)	0.002	0.05	.820	1.1 (0.9-1.4)
Pre-existing asthma (yes/no)	0.034	0.73	.393	1.0 (1.0-1.1)
Total IgE (kU/L)§	0.204	4.44	.036	1.1 (0.8-1.6)
Employed during study (yes/no)	0.017	0.36	.547	1.4 (0.5-3.8)

Note that the age-adjusted relative risks were calculated for the high-exposure group only and numbers in parentheses indicate 95% confidence intervals.

Dichotomization criteria include the following:

*Smokers versus nonsmokers or exsmokers.

†FEV₁ greater than or equal to 90% versus less than 90% of predicted value.

‡Slope less than 15% versus greater than or equal to 15 % · mg⁻¹.

§Less than 100 versus greater than or equal to 100 kU/L.

showed a significant risk for smokers but also a higher risk in newly employed subjects (Table VI).

DISCUSSION

We have shown that Pt salts represent relevant allergens in a catalyst production plant. Both Pt salt sensitization and new allergic symptoms were associated with the degree of exposure. Although both parameters were closely associated, there were subjects with symptoms but without sensitization and vice versa. It is known from the literature that asymptomatic subjects sensitized to Pt salts will inevitably develop allergic symptoms if not transferred to places without exposure.² This could not be investigated in this study because of the intervention that was performed after the detection of a positive skin test response with Pt salt. Little is known about the follow-up of subjects with work-related symptoms but without sensitization to Pt salt. New symptoms in subjects without sensitization were not associated with new sensitization or other disease signs at

follow-up examinations. Thus SPT conversion was a valid outcome parameter in this study.

Selection because of the healthy worker effect may also occur in prospective cohort studies. We established a social program within the plant to avoid the discharge of affected individuals. An immediate job transfer to a division with no exposure took place after sensitization. Subjects who refused participation initially but participated afterward did not show sensitization to Pt salts. Most of the catalyst employees (94.6%) had follow-up examinations, and only 6% of the recruited catalyst staff refused one or more examinations. Although a final examination was not performed in subjects who had left the plant, the somewhat lower percentage of subjects leaving among the group of catalyst employees (Table I) argues against relevant selection.

Risk factors of Pt salt sensitization were exposure and smoking. This finding agrees with findings from 2 recent studies.^{2,10} Atopy was not a significant predicting factor in any of the studies. We were unable to demonstrate that

pre-existing bronchial hyperresponsiveness is a risk factor of sensitization to Pt salt. It is generally assumed that newly employed subjects have a higher risk of having allergies, and occupational cohorts represent selected populations in whom immunity has developed. This study confirms a slightly but not significantly increased risk for beginners.

If one compares the incidence rate of the present study (5.9 per 100 person-years in beginners of the highly exposed category) with that of a recent prospective study in a South African refinery,² the latter is about 4-fold higher (22.8 per 100 person-years). This difference increases further if it is considered that subjects not engaged in the production process were included in the South African cohort. Incidence rates of 28.8 and 7.1 per 100 person-years were reported in 2 historical prospective cohort studies in refineries in the United Kingdom¹⁰ and France,¹¹ both with study periods comparable with those of the present study. The incidences in these studies increase to 34.6 and 14.8 per 100 person-years if only a 2-year observation period is considered. In contrast to these studies, new sensitizations occurred mainly in the third year of employment in our study. Although incidence rates vary somewhat between studies, it is obvious that the rate found in this catalyst plant is lower than that reported from refineries.

Exposure to halogenated Pt compounds occurs both in refineries and catalyst plants. The lower sensitization incidence of our study is probably due to a lower exposure degree in catalyst production. Most hazardous is the impregnation of devices with Pt salt, which is almost entirely performed by robots. An exposure assessment confirmed lower exposure compared with published data in refineries in which airborne soluble Pt values above 2 $\mu\text{g}/\text{m}^3$ were found in up to 75% and 27% of the measurements.^{1,2} Because of the high variability of Pt concentrations in the high-exposure category, a valid cut-off value for occupational hygiene cannot be defined by this study. However, because no sensitization was observed in subjects with low or no exposure, maximal Pt concentrations in these areas (below 10 ng/m^3 soluble Pt or below 100 ng/m^3 total Pt) may be defined as safe.

There is a controversy about the allergenicity of Pt emissions from car catalysts. Pt is emitted in particulate form and is mainly in the oxidation state 0 (elemental Pt).¹² There is strong evidence that elemental Pt is not allergenic and that the allergy-eliciting compounds are confined to the group of ionic complexes containing halogen ligands.^{13,14} However, the emission of soluble Pt cannot be completely excluded. In engine test bench experiments this fraction was about 1% of total Pt.¹⁵ Even if one assumes, as a worst case, that this fraction comprises exclusively halogenated compounds, the dose-response relationship established in the occupational setting described above does not indicate any risk resulting from catalyst-borne Pt in ambient air.¹⁶

Biologic monitoring demonstrated higher serum Pt values in highly exposed subjects. A further interpretation or comparison between categories could not be per-

formed because it has recently been shown that Pt from dental alloys, which were not assessed in our study, may result in higher urine Pt concentrations.¹⁷

In summary, this study demonstrates that Pt salts are relevant allergens in catalyst production plants. Although we have not performed an intervention study to assess the effectiveness of primary prevention, both the lower exposure levels compared with those of precious-metal refineries and the lower incidence of Pt salt sensitization are suggestive of the effectiveness of primary prevention measures in Pt salt allergy.

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