Exposure-response analyses for platinum salt–exposed workers and sensitization: A retrospective cohort study among newly exposed workers using routinely collected surveillance data

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Background: Chloroplatinate salts are well-known respiratory sensitizing agents leading to work-related sensitization and allergies in the work environment. No quantitative exposure-response relation has been described for chloroplatinate salts.
Objective: We sought to evaluate the quantitative exposure-response relation between occupational chloroplatinate exposure and sensitization.
Methods: A retrospective cohort study was conducted using routinely collected health surveillance data and chloroplatinate exposure data. Workers who newly entered work between January 1, 2000, and December 31, 2010, were included, and the relation between measured chloroplatinate exposure and sensitization (as determined by skin prick test responses) was analyzed in more than 1000 refinery workers from 5 refineries for whom a total of more than 1700 personal exposure measurements were available.
Results: A clear exposure-response relation was observed, most strongly for more recent platinum salt exposure. Average or cumulative exposure over the follow-up period was less strongly associated with sensitization risk. The exposure-response relation was modified by smoking and atopy.
Conclusions: Indications exist that recent exposure explains the risk of platinum salt sensitization most strongly. The precision of the estimate of the exposure-response relation derived from this data set appears superior to previous epidemiologic studies conducted on platinum salt sensitization and as a result, might have possible utility for the development of preventive strategies. (J Allergy Clin Immunol 2016;137:922-9.)

Key words: *Sensitization, chloroplatinate salts, exposure response, retrospective cohort study*

Abbreviations used
ACGIH: American Conference of Governmental Industrial Hygienists
AIC: Akaike information criterion
GM: Geometric mean
PGM: Platinum group metals
RR: Risk ratio
TLV: Threshold limit value

Health effects in workers handling halogenated platinum salts were first reported in 1911.[1] Cross-sectional health surveys of platinum refinery workers and in platinum-bearing catalyst production in the past years have shown allergic symptoms affecting the respiratory tract to be common.[2-7] The symptoms are generally those of a type I allergic reaction, and the results of skin prick tests with complex salts of platinum (complex halogenated platinum compounds in which the halogen atoms are directly coordinated to a central platinum atom) were shown to correlate well with symptoms provoked by direct inhalational challenge using the same salts.[8] It has been demonstrated that the complex halogenated platinum salts are allergenic, and the potency appears proportional to the number of halogen ions.[9] Exposure to platinum compounds in which halogen atoms are exclusively ionically associated with and not complexed to the central platinum ion has not been associated with sensitization.[9-12]

The clinical signs and symptoms of the hypersensitivity response in platinum salt sensitization are similar to those provoked by other inhalable or dermal allergens and are not specific to platinum salts. These symptoms include conjunctivitis with itching and lacrimation, rhinitis with nasal obstruction, cough, chest tightness, shortness of breath, and wheezing.[13] The symptoms develop after induction of sensitization response. Thereafter, they usually occur in the allergic subject within a few minutes or hours of exposure, but in some cases the asthmatic response can be delayed and cause nocturnal symptoms. The allergic symptoms indicate a type I reaction mediated by IgE. Complex salts of platinum act as a hapten and through combination with a protein, form an antigen that then stimulates IgE production. T lymphocytes, dendritic cells, and eosinophils, together with the cytokines released by them, are important factors in mediating the allergic response and regulation of IgE.

The American Conference of Governmental Industrial Hygienists (ACGIH) adopted a threshold limit value (TLV) of 2000 ng/m^3 time weighted over a work shift (8 hours) for soluble platinum salts in 1963 in the absence of a clear exposure-response

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relation.[14] This exposure limit value has since been widely adopted and remains in place in most jurisdictions to date. This value was not health based because of the limited air-sampling data available at the time and the absence of an exposure-response relation for sensitization or, more specifically, occupational asthma. The recommendation was based on a qualitative assessment that revealed "…the need to maintain the concentration of airborne chloroplatinate salts as a very low level to protect against the development of respiratory irritation, respiratory allergy, and dermatitis."

Since 1963, a number of studies on chloroplatinates have provided exposure measurements, crudely documenting levels to which workers are exposed, but none were designed to examine the exposure-response relation between chloroplatinate salts and health effects.[5,6,12,15,16]

In a 5-year prospective cohort study exposure to platinum salts was assessed and associated with the incidence of platinum salt allergy by using sensitization measured based on skin prick test response as an outcome.[17] However, the exposure assessment was based on static area samples only, which were relied on exclusively for the key low-exposure group and comprised a data set of modest size. Exposure measurements were performed over the 2 middle years of the 5-year study, and no attempts were made to estimate exposure before inception of the study. The authors themselves stated that a valid cutoff value for an occupational hygiene exposure limit could not be defined by using the study. Ideally, exposure-response studies include exposure data over the whole exposure range, with most measurements allocated preferably to the groups with lower exposure to allow evaluation of no-effect levels or the exact shape of the exposure-response curve when a no-effect level cannot be identified. In 2008, the Dutch Expert Committee on Occupational Standards published a recommended health-based occupational exposure limit of 5 ng/m^3 for chloroplatinate salts (ie, 400 times lower than the ACGIH soluble platinum TLV).[18] This evaluation was solely based on the longitudinal study described before because this was one of the few studies with documented exposure levels.[17]

Apart from occupational exposures, there has been some speculation about environmental exposures occurring to the general population, and the possibility that platinum-containing ambient particulates could theoretically represent a sensitization risk.[19]

The objectives of this study were to use routinely collected retrospective exposure and sensitization data from the platinum-producing industry to characterize the exposure-response relation for work-related sensitization in workers exposed to chloroplatinate salts.

METHODS

Refineries

Seven platinum refineries in South Africa (n = 3), the United Kingdom (n = 3), and the United States (n = 1) were selected in collaboration with the International Platinum Group Metals Association for inclusion in a retrospective cohort study. All refineries routinely measure soluble platinum as a surrogate for chloroplatinate salts for statutory compliance testing and exposure management. In the remainder of the text, we use the term chloroplatinate exposure. These refineries all conducted routine medical surveillance programs designed for the early detection and management of platinum salt sensitization. All 7 were visited by a team consisting of an occupational physician (F.v.R.) and an occupational hygienist (R.H.). The aim of the visit was (1) to perform a walk-through survey that should result in detailed insight into the job titles and tasks performed, potential exposure, and the process; (2) to evaluate exposure assessment practices and health surveillance methodology; and (3) to evaluate data management and storage. Of the 7 refineries, 5 could produce data of sufficient quality within the timeframe of the study. One was a primary refinery processing only locally produced platinum group metals (PGM) concentrate, 3 were secondary refineries processing only recycled PGM-containing materials, and 1 was a mixed facility processing both PGM concentrate and recycled PGM-containing materials.

Exposure data

The walk-through survey showed that processes and work organization differed substantially between refineries, as a result of which no generic job title structure existed across all refineries that would be informative for the experienced exposure levels. Thus site-specific job titles were used for exposure assignment in each plant. These site-specific job titles were defined in collaboration with local occupational hygienists. For each plant, exposure measurements completed between January 1, 2000, and December 31, 2010, were collected and compiled in Excel work sheets by the local hygienists. Only personal time-weighted average measurements based on the inhalable or total dust fraction and taken with portable sampling equipment were included in the exposure database. Area (static) monitoring results were explicitly out of scope because of the exposure characterization errors implicit in such measurement strategies. The following variables were recorded in the database: facility, sample ID, date of measurement, material analyzed, collection methods and method of analysis,[20-23] routine/nonroutine sample, concentration of chloroplatinate salts per filter, sampling time, concentration in nanograms per cubic meter, analytic limit of detection, job title (refinery specific), and workplace. Only samples that had been collected with sampling times of longer than 420 minutes (7 hours) were included. Limits of detection changed from approximately 1000 to 1 ng/m^3 in more recent years, mainly depending on the analytic technique used and to a lesser extent, the air volume sampled over the work shift. Distributions of the platinum salt concentrations were highly skewed, and therefore measurement results were log-transformed. For some refineries, the number of measurements with levels less than the detection limit could be as high as 60%. Values less than the limit of detection were imputed to estimate unbiased average exposure levels for a job title.[24,25] The lower limit for imputation was set to 0, and the higher limit was set to the analytic limit of detection for a particular sample.

Average platinum salt exposure levels were only calculated for job titles with 6 or more measurements. Job titles with less than 6 measurements available were combined with job titles with 6 or more measurements when justified on the basis of the tasks performed or were ranked in between job titles for which 6 or more measurements were available, and the exposure level relative to the bordering job titles was estimated. Based on information on the area worked and tasks performed by workers with each of these job titles, exposure assignment was done on the basis of expert judgment and completed in collaboration with local occupational hygienists. By following this procedure, each job title could be assigned an average level of exposure to chloroplatinate salts.

Health information

Information on sensitization to chloroplatinate salts, atopy, and smoking came from routine health surveillance, which is performed in these platinum refineries in line with an internal protocol of the International Platinum Group Metals Association for chloroplatinate salts established in 2002.[26] This protocol promotes annual evaluations consisting of skin prick testing with platinum salts and a panel of common allergens to test the atopic status of a worker and completion of a symptom questionnaire. In all refineries chloroplatinate salts were used for skin prick testing; an Na_2PtCl_6 solution in saline of 10^{-3} g/mL was used in combination with a negative (saline) and positive (histamine) control. In one refinery a solution of $(NH_4)_2(PtCl_6)$ was used. Atopy was tested by using different common allergens; in most refineries test were done for Bermuda grass, house dust mite, cat, or tree pollen. Wheal diameters were

measured with a Bencard, and a wheal of 3 mm or greater in comparison with the negative control was considered a positive response. For data analysis, atopy was defined as at least 1 positive skin prick test response (wheal size >3 mm) against one of 3 common aeroallergens. Sensitization to platinum salts was defined as a positive wheal greater than 3 mm in size. Smoking habit was defined as current smoking at the start of follow-up.

The refineries included in this study performed annual evaluations, and medical information was stored centrally. Health surveillance data were collected by personnel from the medical service at each refinery. In some cases records were compared with personnel archives to ascertain all eligible workers. Data were entered at each refinery by making use of prestructured EpiData files, a freeware data entry program (version 2.0, www.epidata.dk). The data were entered by local refinery personnel, and the software was supplied by the research team from Utrecht University. Local personnel received detailed instructions to facilitate harmonized data collection and decide on eligibility of the employees for inclusion in the cohort. Workers present on January 1, 2000, were included in the cohort. For these workers, follow-up was complete until January 1, 2011. For each worker, a record was filled in with pre-employment data, including information about atopic status at job entry, respiratory and other symptoms, job title, smoking habits, sex, and age. An additional record was filled in when either the exposure status changed (transfer to a new job title category) or when sensitization to platinum salts was observed during one of the annual surveys. This approach limited the number of records to be completed but produced an accurate reconstruction of the job history and the year sensitization occurred.

Exposure and health data were sent to the coordinating center for further processing. Linkage between personal identifiers and study data were kept at the refineries. Consistency of the data entered and transferred was checked. In case of inconsistencies, local personnel were contacted to solve any issues. Exposure and surveillance data were compiled in 2 pooled data sets.

The study protocol, as well as central data management and data processing, were approved by local medical ethics committees in the respective countries: the Human Research Ethics Committee of Witswatersrand University, Johannesburg, South Africa; the Health and Safety Executive's Ethics Committee in Bootle, Merseyside, United Kingdom; and the Essex Institutional Review Board in Lebanon, NJ, for the United States.

Data analysis

Because subjects could enter the cohort after the starting date (late entry) of January 1, 2010, exposure could change during follow-up, and right censoring could occur because of study withdrawal (leaving a refinery) or development of sensitization. For analysis, the whole follow-up period is split into so-called risk sets on the basis of each time a censoring event occurs. For the entire cohort, 69,742 risk sets were generated, an average of approximately 67 per subject. For each risk set, the risk for sensitization can be calculated. Integration of the risk for each risk set over the whole follow-up period leads to a hazard function. The exposure of each subject in a risk set was determined on the basis of the job title during the time period of the risk set. When relating exposure for subjects in each risk set to sensitization risk, this procedure implies that "recent or current" exposure at that time (ie, exposure for the time interval of any given risk set) is associated with sensitization risk. The exposure can also be "lagged," which means that sensitization can be associated with exposure in earlier periods. In addition, other exposure variables were considered, such as average exposure and cumulative exposure over the follow-up period.

Risk sets were obtained from crude data by using the free statistical package R (http://www.r-project.org/). Descriptive statistics and survival analysis was conducted in SAS software, version 9.2 (SAS Institute; Cary, NC), as well as in R (for graphics). Penalized splines were calculated in the statistical package R by using the COXPH procedure, as described in the literature.[27,28] For survival analysis, time since job entry was used as a time variable in Proc PHREG in SAS software and with sensitization as an end point. Initially, potential confounders (age and smoking habit at baseline and sex) were included in the models together with categorized or continuous exposure variables to explore associations with sensitization. A pooled analysis was conducted, combining the data from each of the refineries and adjusting for refinery.

TABLE I. Number of measurements and measurements less than the limit of detection, estimated average exposure level (geometric means), geometric SDs, minimum and maximum levels, and percentiles by platinum refinery in nanograms per cubic meter

Refinery	No.	<LOD	GM	GSD	Min	P25	P75	P95	Max
1	203	60	169	7.2	0.29	47	561	4,704	12,000
2	135	41	219	11	0.20	53	900	6,100	19,3375
3	438	272	91	7.4	0.04	24	350	1,538	33,580
4	373	144	79	6.4	0.11	25	278	1,450	12,860
5	463	264	107	13	0.03	19	465	11,300	14,2000

GM, Geometric mean; *GSD*, geometric SD; *<LOD*, less than the limit of detection; *Max*, maximum; *Min*, minimum; *P25*, 25th percentile; *P75*, 75th percentile; *P95*, 95th percentile.

Results from a pooled analysis might produce biased results when average exposure levels differ strongly between refineries, causing ecologic bias. However, by comparing stratified analyses, meta-analyses, and the pooled analysis, we could evaluate whether such a bias potentially occurred. A meta-analysis was conducted in STATA 10.1 software. Linear associations between current exposure and sensitization were calculated for each refinery. Subsequently, effect estimates, expressed per 100 ng/m^3 of chloroplatinate dust, were combined, and heterogeneity by refinery was explored ($P > .10$) by using standardized methods for the random-effects meta-analysis.

The Akaike information criterion (AIC) was used to compare model fit and help to select the optimal smoothing parameter. Biologic plausibility (ie, monotonicity) was considered along with the AIC in selecting the optimal *df* of a spline. Splines were produced for current, average, and cumulative exposure. Finally, exposure lagging was explored, which implies that when sensitization risk in a certain risk set is considered, the risk is associated with exposure during an earlier period. Exposure lagging was performed in discrete steps of 0.5 years. In all data analyses, only subjects who started working after January 1, 2000, were included.

RESULTS

In total, 1763 exposure measurements were available for analysis. Overall geometric mean levels of chloroplatinate are given per refinery in Table I. To a large extent, these differences in exposure levels reflect differences in the process applied to refine platinum from primary or secondary sources and differences in the presence of exposure control technology. The number of measurements with nondetectable chloroplatinate levels were high per refinery, ranging from 30% to 62%. In more recent years, lower analytic limits of detection in the low nanograms per cubic meter range could be reached. In these more recent years with lower analytic detection limits, nondetectable levels reflect low to very low exposure or potentially even absence of particulate exposure.

Descriptive information for the population is given in Table II. Overall, information was available for more than 2000 workers, and the population size varied from around 100 to more than 1000 between refineries. Little more than 50% (1040) of all subjects started working since January 1, 2000. These workers were selected for subsequent analyses to avoid potential biases related to unknown exposures before inclusion in the study cohort. The number of newly hired workers between 2000 and 2010 was 1040, but for 4 of these workers, no information about their job history was available, or they had a job title for which no exposure estimate could be generated, leading to a cohort of 1036 newly exposed workers. Of these, the average age was around 30 years

TABLE II. Descriptive information for the pooled platinum refinery population

Variable	n/N	Percent
All	1040/1040	100
Refinery		
1	164/1040	15.8
2	168/1040	16.2
3	57/1040	5.5
4	135/1040	13.0
5	516/1040	49.6
Sex		
Male	876/1040	84.2
Female	164/1040	15.8
Atopy		
Unknown	89	
No	570/951	60.0
Yes	381/951	40.0
Smoking		
Unknown	14	
No	824/1026	80.7
Yes	198/1026	19.3
	Average	**SD**
Age at baseline (y)	32.4	9.9 (17-72)

TABLE III. Number of sensitized cases, person years of follow-up, and sensitization incidence rates for refinery, chloroplatinate exposure, and some potentially modifying variables in a cohort of platinum refinery workers

Variable	No. of cases	Person years	Rate/100 person years
All	98	4091	2.4
Refinery			
1	12	684	1.75
2	22	677	3.25
3	2	252	0.79
4	12	517	2.23
5	50	1962	2.55
Current exposure (ng/m^3)			
≤49	30	2004	1.49
>49-≤100	19	831	2.29
>100-≤252	27	721	3.74
>252	22	535	3.05
Average exposure (ng/m^3)			
≤51.1	25	1920	1.30
>51.1-≤105	26	1100	2.36
>105-≤250	23	426	5.40
>250	24	645	3.72
Cumulative exposure (ng/m^3·y)			
≤91.6	25	1826	1.40
>91.6-≤172	24	639	3.76
>172-≤452	24	805	2.98
>452	25	822	3.04
Sex			
Male	92	3480	2.64
Female	6	612	0.98
Atopy			
Unknown	2	373	0.56
No	45	2357	1.96
Yes	51	1524	3.46
Smoking			
Unknown	0	76	0
No	66	3066	2.15
Yes	32	791	3.94

for most of the sites, with a clearly higher age in one site (refinery 4) and a clearly lower age in another site (refinery 5). The percentage of smokers and atopic subjects was more or less comparable with the general population in the respective countries in refineries 1 and 5. Clearly different patterns were seen for the other refineries, especially for refinery 3, where the prevalence of atopy and smoking was considerably lower, most likely because of pre-employment selection practices.

Incidence rates for platinum sensitization overall and by exposure category are shown in Table III. On average, subjects were followed for 3.9 years. On average, cases became sensitized after 2.5 person years of follow-up, with a minimum of 0.36 (almost 4½ months) and a maximum of 9.9 years. Overall, 2.4 cases were seen per 100 years of follow-up, with clear differences between refineries in sensitization rates but also between exposure categories between atopic and nonatopic subjects, smokers and nonsmokers, and men and women. Site 3 had the lowest sensitization rate, and this was also the site with the lowest prevalence of atopy and rigid pre-employment selection of nonsmokers at baseline for employment. At site 5, the atopy prevalence was similar to that of the general population, but the smoking prevalence at baseline was relatively low. A restrictive policy during pre-employment evaluations was not the reason for this low prevalence but merely reflects he limited smoking habits of this refinery population, which consisted to a large extent of native Africans.

Survival modeling of incidence data showed that exposure-response relations were observed for "current" exposure, as well as average and cumulative exposure (Table IV). The correlation between current and average exposure was very high (0.98), and thus associations between these exposure proxies and the incidence of sensitization can only be marginally different. The correlation between cumulative exposure on the one hand and current and average exposure on the other hand was considerably lower (0.72 and 0.74, respectively). Thus workers were reclassified considerably when using cumulative exposure instead of current or average exposure. For all 3 exposure measures, a gradually increasing risk was observed with increasing exposure, but for average exposure, the risk was reduced in the highest exposure category. Statistical fit of the models did not differ strongly between the different models, with a tendency of stronger fit for the categorical model with cumulative exposure and a stronger fit for current exposure as a continuous variable in the model. The risk ratios (RRs) for both atopy and smoking were statistically significantly different from 1, with RRs of between 1.5 and 2. Sex also seemed to modify the sensitization risk (univariate RR, 2.8 [95% CI, 1.2-6.4]; $P < .05$), but the coefficient became statistically nonsignificant after adjusting for exposure, indicating that the effect for sex was exposure related. Male subjects were generally more highly exposed and as a result probably had a greater sensitization risk, which explains the increased RR for sex and the fact that this RR became insignificant after adjustment for exposure. Thus sex was not introduced as a parameter to the final models. No residual effects caused by refinery characteristics were observed when sensitization was explained based on exposure, atopy, and smoking at baseline in a multiple regression model. Differences existed between refineries in analytic approaches of, for example, chloroplatinate salts, sampling

TABLE IV. RRs for atopy, smoking, and exposure obtained by using multiple regression analysis results for current, average, and cumulative exposure and platinum salt sensitization

Variable	Current exposure		Average exposure		Cumulative exposure	
Model fit	AIC	1202		1193		1200
Atopy	0/1	1.8 (1.2-2.8)†		1.8 (1.2-2.7)†		1.8 (1.2-2.7)†
Smoking	0/1	1.9 (1.2-2.8)*		1.7 (1.1-2.7)*		1.8 (1.2-2.8)†
Exposure	≤49 ng/m^3	1 (reference)	≤51.1 ng/m^3	1 (reference)	≤91.6 ng/m^3·y	1 (reference)
	>49-≤100 ng/m^3	1.4 (0.8-2.6)	>51.1-≤105 ng/m^3	1.8 (>1.0-3.2)†	91.6>-≤172 ng/m^3·y	2.7 (1.5-4.8)‡
	>100-≤252 ng/m^3	2.2 (1.3-3.8)†	>105-≤250 ng/m^3	4.2 (0.9-48)*	172>-≤452 ng/m^3·y	2.3 (1.2-4.1)*
	>252 ng/m^3	3.2 (1.9-5.7)‡	>250 ng/m^3	3.0 (0.8-44)*	>452 ng/m^3·y	3.8 (2.0-7.1)‡
Model fit	AIC	1208		1208		1213
Atopy	0/1	1.8 (1.2-2.6)*		1.8 (1.2-2.7)†		1.8 (1.2-2.7)*
Smoking	0/1	2.0 (1.3-3.1)†		1.7 (1.1-2.6)*		1.7 (1.1-2.6)†
Exposure	Expressed per 100 ng/m^3	1.18 (1.1-1.3)‡	Expressed per 100 ng/m^3	1.17 (1.1-1.3)†	Expressed per 100 ng/m^3·y	1.4 (>1.0-1.9)*

*$P < .05$.
†$P < .005$.
‡$P < .001$.

procedures (inhalable vs total dust), and skin prick test responses. Adjustment of the exposure-response relation for refinery in the models did not change regression coefficients for exposure or the other included variables. Thus refinery was kept out of the final models as well. Age was not associated with sensitization and was not included in the models either.

Interactions between atopy and exposure and smoking and exposure did not yield statistically significant interaction variables in addition to the main effects for exposure, atopy, and smoking, respectively. Thus the final model contained atopy, smoking, and exposure as main effects only. A random effects meta-analysis, in which a meta-exposure-response slope was calculated on the basis of a linear model of exposure and sensitization for each refinery, was not indicative of heterogeneity between refineries (data not shown).

Analyses using penalized splines generally produced a more refined picture than analysis with categorical exposure data. A clear monotonic increasing exposure-response relation was seen for current platinum salt exposure up to a level of 200 ng/m^3 (Fig 1, *A*) and a leveling off at considerably higher exposure levels. Average exposure resulted in a similar exposure-response relation, but there was a tendency toward a slightly reduced risk at very high exposure levels (Fig 1, *B*). The use of cumulative exposure as an exposure proxy led to considerable recategorization of the population, and this resulted in a clear bell-shaped exposure-response relation (Fig 1, *C*). After a peak in sensitization risk between 1000 and 2000 ng/m^3 per year, the risk was clearly reduced at higher cumulative exposures, indicating that susceptible subjects had become sensitized and were probably exhausted in the population, resulting in a survivor population. The fit of this relation was less strong than observed for current and average exposure. Plotting the hazard function over time of follow-up for the whole population indicated that the risk of becoming sensitized peaked between 500 to 600 days since employment and thus after initial exposure to chloroplatinate salts (Fig 2, red line shows the population average).

Lastly, the exposure was lagged by 0.5, 1, and 1.5, and so on, to 5 years. Lagging of exposure for risk sets early during follow-up requires an estimate of exposure before subjects were included in the cohort. Here the choice is either to assign a value of 0 to exposure, which might be incorrect because these subjects could have worked in other refineries, or to remove the risk set involved from the analysis. In the latter case a comparison with unlagged analyses would be incorrect because the number of risk sets differs between lagged and unlagged exposure analyses, which in itself influences model fit. Both approaches were explored, and the first exposure before employment was assumed to be 0. For the second approach, a fair comparison of model fit was obtained by removing similar risk sets from the lagged and unlagged exposure data set. For both approaches, similar trends were observed in results. In general, model fit differed modestly between lagged and unlagged models. Differences were moderate because only a limited number of workers (approximately 19%) changed job title over the follow-up period. Thus the assigned exposure level changed for only a limited number of subjects because of lagging. This analysis indicated that sensitization risk was determined more strongly by exposures that occurred 1 or 2 years before sensitization than exposures that occurred further away in the past. For instance, for the spline model with 3 *df*, the nonlagged model and the models lagged by 0.5 and 1.0 years had comparable models fits (AIC, 1195-1197). However, when the lagging was increased to 1.5 years and more, the AIC increased distinctly (AIC, 1208), indicating a clearly reduced model fit for the model lagged by more than 2.0 years. Thus fairly recent exposures seem to explain sensitization risk more strongly than earlier exposures. For cumulative exposure, associations between exposure in the most recent 1 or 2 years led to associations that were almost similar to those for current exposure.

DISCUSSION

A clear quantitative exposure-response relation for chloroplatinate salts and specific sensitization was observed in this longitudinal study among platinum refinery workers. The exposure-response relation for current exposure is characterized by an initial steep increase in risk starting at low exposure levels and leveling off at levels of greater than 200 ng/m^3 for current exposure (Fig 1, *A*). Bell-shaped exposure-response relations were observed for cumulative exposure, suggesting a strong survivor effect at higher cumulative exposure levels. Lagged analyses indicated that more recent exposure determines the risk for sensitization more strongly than exposures further back in

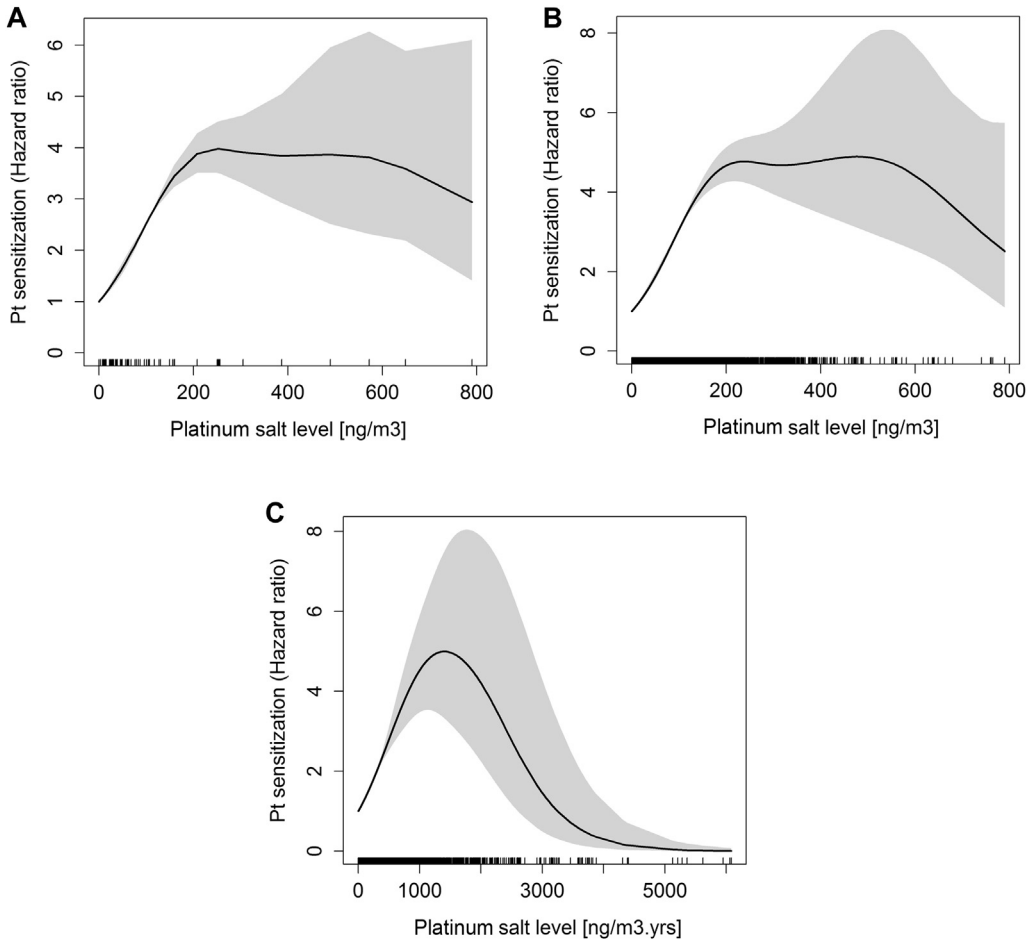

FIG 1. Penalized splines for association between sensitization and exposure in a cohort of platinum *(Pt)* refinery workers adjusted for atopy and smoking: **A,** current exposure; **B,** average exposure; **C,** cumulative exposure.

time, although the differences in fit between the different models were modest. The risk for chloroplatinate sensitization appeared highest after 500 or 600 exposure days maximally and then gradually decreased. However, these results should be interpreted with care because the moment sensitization occurred has been measured with considerable imprecision because surveys were conducted on an annual basis only.

The overall sensitization rate in this study was 2.4 per 100 person years of follow-up. This is lower than the rates observed in earlier longitudinal studies, which found rates of between 22.8/100 person years and 5.9/100 person years in 1995 and 2000, repectively.[15,17] These 3 studies suggest a gradual decrease in risk from 22.9/100 to 5.9/100 to 2.4/100 between 1995 and 2010. Although exposure was not characterized in detail in the earlier published studies, there are indications that levels were higher, especially in the study published in 1995. In the first study 27% of the samples had levels above 2000 ng/m^3 (the ACGIH TLV).[15] In the more recent study 4% of the samples had levels above the ACGIH TLV, which is on the same order of magnitude observed in our study, where 8.5% of the samples had TLV values greater than 2000 ng/m^3. Unfortunately, information about only the tail of the distribution does not allow a more refined comparison of average levels across different (sub)populations. Differences in sensitization rates might be the result of differences in exposure to chloroplatinate salts. However, differences in the numbers of atopic subjects and smokers might have contributed as well.

The observed exposure-response relation was modified by atopy and smoking, with RRs of between 1.6 and 1.8 for atopy and smoking, respectively. Effect modification seems less strong than usually found in the literature for other allergens, probably because the effect of atopy has been most often assessed in cross-sectional studies in which cross-reactivity between occupational and common allergens cannot be excluded or because sensitization to an occupational allergen is paralleled to sensitization against a common allergen. On the other hand, the estimates of the effect of smoking and atopy should be carefully interpreted because of pre-employment selection in varying degrees of intensity across most of the refineries. Other studies generally observed larger RRs for smoking of between 3.9 and 8.0.[15,17,29] In a recent cross-sectional study smoking was not associated with chloroplatinate sensitization.[9] The reasons for the different estimates for the effect of smoking are not known, but in most studies associations with smoking were not exposure adjusted. This might have contributed considerably, especially in some earlier studies, when exposure was higher than at present.

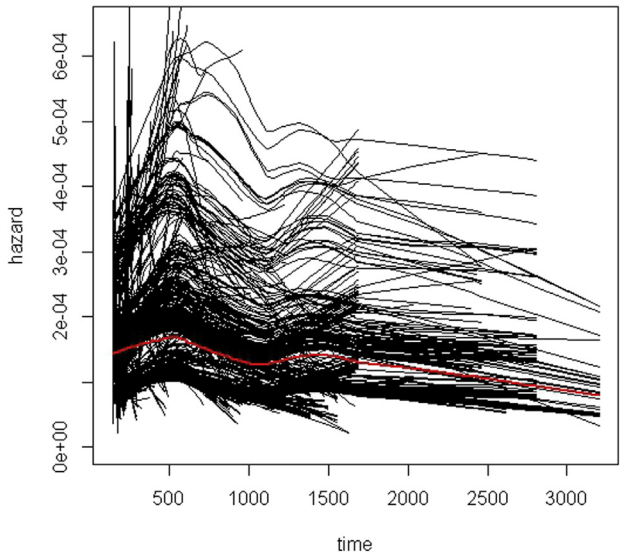

FIG 2. Hazard plot for sensitization against follow-up (time in days) for each subject (*black lines*; average population member with regard to smoking and atopy) and the population *(red line)*.

For atopy, similar relative risks of between 1.1 and 2.3 were observed.[15,17,29]

Results of the exposure-response analysis provided some important new insights. A considerably stronger association with a considerably better statistical fit was observed for exposure in the most recent period preceding sensitization than for current average exposure or cumulative exposure over the whole follow-up period. The observation that current exposure, preceding sensitization by 1 to 2 years maximally, determines the risk more than cumulative exposure has not been reported before for any other (occupational) allergen. Most exposure sensitization studies have thus far been cross-sectional, and the few longitudinal exposure-response studies available did not consider different exposure proxies in the analysis, even if exposure data were available.[30] Earlier studies on platinum sensitization either did not have exposure data over a long period of follow-up and were thus not able to perform analysis for a cohort with different proxies of exposure or did not exhaust the use of the exposure data optimally.

Exposure to platinum salt allergens occurs in the form of particulate exposure. The risk for sensitization is already increased in the low nanogram per cubic meter range. Such levels can be reached easily after exposure to a limited number of particulates of a few micrometers. Such exposures can be realized already during short-term activities, as has been observed for enzyme allergy exposure in bakeries and in the enzyme industry, as well as house dust mite exposure.[31-33] For high-molecular-weight sensitizers, such as house dust mite allergen and purified enzymes, sensitization also occurs at low levels in the low nanogram per cubic meter range.[32-34] It has been suggested that sensitization against work-related allergens might be the result of peak exposures.[35] Exposures in the low nanogram range can easily occur during short periods when tasks are being performed during which relatively high numbers of particulates are released in the air.

When peak exposures are important, it could be more relevant to consider the likelihood of high exposures by using the available exposure data in a more refined way. This was considered in a sensitivity analysis by taking the 75th and 90th percentiles of the job title–specific exposure distributions as a proxy of exposure instead of the geometric mean exposure but did not lead to stronger associations with sensitization. More detailed exposure data, in particular at lower exposure ranges, might be required. Improving the exposure assessment component by using more sensitive analytic techniques in combination with speciation of different forms of platinum is justified and would contribute to a better insight in the sensitization risk from chloroplatinate exposure at lower levels. It is not clear whether dermal exposure plays a role in the development of respiratory sensitization, which has been suggested for some other allergens. Dermal exposure assessment might also be considered as an additional component, which can be included in more refined exposure assessment studies. In addition, exposure assessment was most often based on compliance strategies focusing on the more highly exposed workers. Strategies focused more on random sampling–type approaches or even allocation of a higher measurement effort to the fraction of this population with lower exposure would have resulted in more precise exposure estimates for workers with lower exposure.

The study has a few potential weaknesses. Although changes in exposure were considered in the analysis by comparing different exposure proxies and lagged and unlagged models, changes in smoking habits and atopy were not considered. This might have resulted in somewhat diluted associations. Information about smoking habits and atopy during the employment period was not recorded consistently in all refineries. Improving surveillance compliance will benefit more refined statistical analyses in the future.

A major issue is the pre-employment selection in some of the plants for smoking and atopic responses to common allergens. It is important to realize that smoking and atopy are known modifiers of the relation between platinum salt exposure and sensitization. Removal of atopic subjects and smokers from the eligible work force will have reduced the absolute risk for sensitization and will have shifted the exposure-response relation to the right or will have made the relation less steep. On the other hand, sensitivity analysis on the basis of only refinery 5, where no pre-employment selection took place, revealed the same patterns for the associations between exposure and sensitization, as described for the pooled analysis in this study. In this plant smoking and atopy were determinants of sensitization, and risk estimates differed only to a very limited extent.

It is possible that an exposure threshold exists at which the risk for becoming sensitized exists at a very low exposure level. In most refineries, especially highly exposed workers have been sampled more often. Exposure estimates for subjects with job titles resulting in low exposure are less precise and subject to estimation error, also because of the high number of measurements less than the limit of detection. As a result, the shape of the exposure-response relation at the low end of the exposure distribution could deviate from what is shown in this study. This remains the region of greatest uncertainty in the exposure-response characteristic. Exposure estimates at the low end of the distribution could be improved by allocating more measurement effort to the lower exposure ranges. This will facilitate a refined analysis focusing on the shape of the exposure-response relation.

In conclusion, a clear quantitative exposure-response relation was observed for chloroplatinate salt exposure, with clearer associations for more recent exposures. The association was modified only modestly by smoking and atopy. Results from this study have possible utility to preventive strategies.

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Key messages

- **A clear exposure-response relationship was observed for occupational chloroplatinate exposure and platinum sensitization.**
- **Exposure in more recent years before sensitization seemed more relevant than exposure further back in the past.**

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