# 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 2015;■■■:■■■-■■■.)**

***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