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## Exposure-response relationships for platinum salt sensitization in precious metal refinery workers: a 16-year retrospective study

Background: Occupational exposure to soluble chlorinated platinum (Pt) salts, commonly called chloroplatinates, is a known cause of Pt salt sensitization (PSS) and occupational asthma. When PSS has been established, sensitized workers are usually redeployed to jobs with low chloroplatinate exposure levels or environments without exposure to prevent development of occupational allergy and asthma.

Objectives: We aimed to model inhalable soluble Pt salts exposure levels based on measurements in precious metal refineries for use in a retrospective cohort study on PSS, and assess the exposure-response relationship between soluble Pt salts exposure and PSS in a 16-year retrospective cohort study (2000-2015).

Methods: We analyzed routinely collected exposure levels and medical surveillance data from five platinum refineries located in the United Kingdom (3 sites), United States, and South Africa. The refineries provided time weighted average inhalable soluble Pt salts exposure data, measured in 2,982 personal air samples. We used a Bayesian hierarchical model to estimate geometric mean (GM) exposure levels for each refinery and job title over time. In total, 1,614 newly hired workers who entered the industry since 2000 regularly underwent skin prick tests. The relationship between time-varying exposure levels and PSS development was analyzed by Cox proportional hazards regression, adjusting for smoking, atopy, and facility.

Results: The GM of measured exposure levels over all facilities was 92 ng/m3 with a geometric standard deviation (GSD) of 9.07. Facility-specific GMs ranged from 48 ng/m3 (GSD 15.3) to 242 ng/m3 (GSD 5.99). Exposure modelling showed that soluble Pt salts exposure levels declined approximately 10% per year in two of the five facilities, but there were no clear time trends in the other facilities. A priori specified exposure groups captured most of the between-jobs differences, which helps to accurately predict exposures for jobs with no measurement data available. PSS was diagnosed in 117 workers (1.48 per 100 person-years of follow-up time) with median time to PSS of 1.9 years, and with an estimated median exposure level of 53 ng/m3 (P5-P95: 8-302 ng/m3) at the time of PSS development. Statistically significant quantitative exposure-response relationships between PSS and cumulative and current exposure were found. Exposure-response curves showed a steep increase in PSS incidence at exposure levels up to 100 ng/m3, with no or only a slight further increase at higher levels.

Conclusions: We found a clear exposure-response relation between soluble Pt salts exposure and PSS incidence among newly hired workers. Despite the limitations inherent to the retrospective study design, this cohort study contributes to the growing body of evidence that the widely adopted occupational exposure limit of 2,000 ng/m3 does not adequately prevent PSS and should be re-evaluated.

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