

Medical surveillance and long-term prognosis of occupational allergy due to platinum salts

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Abstract

Purpose Medical surveillance of workers in precious metals refineries and catalyst production plants is well established in many countries as a measure to prevent occupational asthma due to platinum (Pt) salts. It was the aim of this study to evaluate the impact of medical surveillance and to define prognostic factors with an emphasis on exposure determinants.

Methods As part of an observational longitudinal study, 96 workers from German precious metals refineries and catalyst production plants with Pt salt allergy underwent a second examination several years (median 67 months) after the initial diagnosis was made.

Results When the second examination was conducted, 92 subjects (96 %) had already been transferred to jobs with very low or no exposure to Pt salts. The number of subjects with sensitization to Pt salt as assessed by skin prick test (SPT_{Pt}) decreased from 86 to 52 %, and there was a clear improvement for rhinitis, conjunctivitis and contact urticaria between both examinations. Although the number of subjects with asthma symptoms decreased significantly, at the second examination 74 subjects (77 %) continued to suffer from asthma and 51 subjects (53 %) received asthma medication. Airway obstruction or bronchial hyperresponsiveness persisted in 83 subjects (86 %).

Conclusions Secondary prevention in subjects with occupational exposure to Pt salts, as practiced for over 25 years in Germany could not avoid persistent asthma in the

majority of cases, although improvements occurred. This study reveals the limitations of the concept that removal from exposure after the occurrence of respiratory symptoms may prevent chronic asthma. It is recommended that removal from exposure should be done immediately after the occurrence of a positive SPT_{Pt}, irrespective of symptoms.

Keywords Asthma · Exposure cessation · Platinum salts · Occupational · Prognosis · Surveillance

Abbreviations

CI	Confidence interval
IgE	Immunoglobulin E
FEV ₁	Forced expiratory volume in one second
IPA	Institute for Prevention and Occupational Medicine of the German Social Accident Insurance, Institute of the Ruhr University Bochum
OA	Occupational asthma
OR	Odds ratio
Pt	Platinum
SPT	Skin prick test
sRt	Specific airway resistance

Introduction

Data on the long-term outcome of occupational asthma (OA) are sparse, but one common finding is that prognosis remains poor (Rachiotis et al. 2007; Ameille and Descatha 2005). Less disease severity at diagnosis (Ameille and Descatha 2005; Padoan et al. 2003) a short duration of ongoing exposure after the occurrence of symptoms (Rachiotis et al. 2007) and a long duration of follow-up (Malo and Ghezzo 2004) are considered significant predictors for a

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favorable outcome. Conversely, the contribution of other factors, such as type of allergen (high vs. low molecular weight), medication or atopy remains controversial.

Despite the small number of systematic evaluations done on medical surveillance programs, a recent review concluded that the available evidence supports beneficial effects, including those interventions directed at reducing exposure (Wilken et al. 2012). However, the different tools used for the detection of early disease and the disparities in the frequency of examinations make it difficult to determine whether such programs are indeed effective. Furthermore, the type of intervention implemented is also relevant. Because complete cessation of exposure often has severe socioeconomic consequences, one frequent option is to reduce exposure. However, a recent review concluded that the reduction of exposure cannot be routinely recommended as an alternative to the cessation of exposure in the management of occupational asthma (Vandenplas et al. 2011). Additionally, asthma medication and the use of respirators seem to be of limited value (Vandenplas et al. 2012).

Medical surveillance for incident OA due to platinum (Pt) salts has a long tradition in platinum refineries and catalyst production plants. A highly sensitive and specific skin prick test with Pt salt (SPT_{Pt}), usually performed once a year, is an ideal tool for surveillance. The interventions in subjects with a positive SPT_{Pt} are various. Whereas a large number of subjects are transferred to other areas within the plants that are free of Pt salts in order to limit exposure or leave the company, it is common practice to transfer highly qualified operators to adjacent rooms or departments. In a previous retrospective cross-sectional study, we described the outcome of OA due to Pt salts, concluding that subjects transferred to low exposure jobs had a similar prognosis to those who were completely removed from exposure (Merget et al. 1999). However, a definite conclusion was difficult due to the cross-sectional design of the study.

In the present manuscript, we report on longitudinal data from subjects with diagnosed occupational Pt salt allergy. The overall aim was to evaluate the long-term prognosis of the workers who were sensitized or allergic (asthma, rhinitis, conjunctivitis and contact urticaria) to Pt salts, and to possibly define the factors associated with a favorable prognosis.

Methods

Subjects

Medical surveillance of workers at risk of Pt salt allergy is not mandatory in Germany. However, most plants performed yearly examinations of their workers using questionnaires and SPT_{Pt}, but this was not the case in all plants

or during the whole study period. It was the plant physicians' decision to refer subjects with a positive SPT_{Pt} to our institute (IPA) for a diagnostic evaluation. IPA forwarded the results of the examination to the compensation boards, the members of which considered each case for compensation. The compensation boards initiated follow-up examinations, usually at IPA; however, the workers were free to choose the institution that performed the follow-up examination. Follow-up examinations were terminated if the subjects were no longer exposed to Pt (thus worked in very low or no exposure areas), had no allergic symptoms, and showed normal lung function. A total of 125 subjects with Pt salt allergy were examined, among them 96 workers from eight German precious metals refineries and two catalyst production plants who underwent at least two examinations between 1983 and 2008. Seventy-six workers (79 %) were recruited from two refineries. Sixty-one subjects (64 %) had been included in an earlier cross-sectional study (Merget et al. 1999). The initial examination took place in the 1980s ($n = 22$), the 1990s ($n = 60$) or later than 2000 ($n = 14$).

If more than two examinations were performed, only the first and the last examinations were considered. At the first examination, 93 subjects (97 %) reported work-related new-onset allergic symptoms, thus asymptomatic SPT_{Pt} positivity was found in only three cases. The diagnosis of Pt salt allergy was corroborated with a positive SPT and/or a positive inhalative challenge, using Pt salt in each case. Nine subjects did not show a positive SPT_{Pt} at any examination, but were diagnosed using a positive inhalative challenge. Four subjects with a negative SPT_{Pt} at the first examination had a positive result at the second examination. All subjects signed informed consent for the tests, and the test procedures were approved by the ethics committee of the Johann Wolfgang Goethe University, Frankfurt.

Selection

Twenty-nine subjects with Pt salt allergy were lost in the follow-up after diagnosis. Although asthma symptoms were less frequent among these subjects than in the study group (31 vs. 91 % at the first exam), FEV₁ (mean 91 vs. 92 %pred.) and the number of subjects with airway obstruction or bronchial hyperresponsiveness (72 vs. 90 %) were similar. Also, the outcomes in subjects after two examinations ($n = 39$) were not different from those with more than two examinations ($n = 57$) (data not shown).

Exposures

Refinery and catalyst workers had complex and variable exposures to not only chloroplatinates, but also to insoluble compounds, such as PtO, PtO₂ and others. Workers were

also exposed to irritants, such as chlorine, acids, vanadium and other metal compounds. Although adverse effects of these substances cannot be excluded, it is our experience that airway symptoms are closely associated with Pt salt allergy. Thus, exposure to irritants was not considered in this study.

The monitoring of airborne Pt concentrations was not performed on a regular basis by the plants, thus we used the same exposure categories as reported previously (Merget et al. 1999). Briefly, ‘high exposure’ was defined as workplaces where subjects acquired new work-related symptoms, usually in production, but also in quality control and in laboratories. Available data indicate that soluble Pt air concentrations in high exposure areas may exceed $0.2 \mu\text{g}/\text{m}^3$, rising to levels above $2 \mu\text{g}/\text{m}^3$, the former threshold limit value (TLV) for soluble Pt in Germany. ‘Low exposure’ was defined as workplaces adjacent to high exposure areas, usually within the same building with air concentrations in the range of $20\text{--}200 \text{ ng}/\text{m}^3$. ‘Very low exposure’ areas were defined as workplaces within the plant that were not in the vicinity of high exposure areas. All air concentrations of soluble Pt in these areas were measured below $20 \text{ ng}/\text{m}^3$. These soluble Pt air concentrations were defined by one large refinery and are part of the case management recommendation that is proposed by the German Accident Insurance (DGUV Information 240–130; in preparation). Subjects who had left the plant were assigned to ‘no exposure.’ A recent study with 1763 exposure measurements in five refineries reported the 25th percentiles in a range between 19 and $53 \text{ ng}/\text{m}^3$, which would be defined as ‘low exposure’ in the present study (Heederik et al. 2016).

History and general medical investigations

Personal data and information about smoking, atopy, asthma prior to exposure, exposures at work, current symptoms and medication were obtained by a questionnaire and a physician interview (the first author throughout the study, with few exceptions). In addition, we asked for new-onset symptoms at work at the time of diagnosis. Asthma was defined as affirmation of the questions about shortness of breath and if yes whether it was variable, rhinitis as recurrent runny nose or sneezing, and conjunctivitis as recurrent itching or burning eyes. Skin complaints were recorded if no obvious non-occupational diagnosis was evident (e.g., psoriasis). Besides the dates of both examinations, the start of exposure to Pt salts, incident work-related symptoms suggestive of Pt salt allergy, duration of work in each exposure group, time from the onset of symptoms to the interventions (transferal to low, very low or no exposure areas), as well as the time periods between these exposures and the examinations were recorded. All subjects underwent a physical examination, standard blood analyses, chest X-ray

and electrocardiogram, but no relevant non-occupational cardiopulmonary diseases were detected.

Lung function

Spirometry was performed with MasterLab, CareFusion, Würzburg, Germany. At least three acceptable maneuvers were obtained; since 1995, the American Thoracic Society’s recommendations were established (ATS 1995). The European Community for Steel and Coal reference values were chosen (Quanjer et al. 1993). Methacholine testing was modified twice during the observation period. Up until 1993, one particular method was used as previously published (Merget et al. 1991). From 1993 until 2001, doubling doses of methacholine were used with the same method. However, the method changed in 2001, where methacholine testing was performed using a reservoir method as described recently (Polychronakis et al. 2013).

Allergy testing

Total immunoglobulin E (IgE) was measured in sera by standard tests (which varied during the study). SPT with a battery of 18 or more environmental allergens from various manufacturers and Pt salt were performed as previously described (Merget et al. 1991). Atopy was defined as a wheal diameter of $\geq 4 \text{ mm}$ with any environmental allergen. Hexachloroplatinic acid (H_2PtCl_6) up to 10^{-2} mol/L ($\sim 4 \text{ g/L}$) was used for SPT_{Pt} until 1993. Afterward, sodium hexachloroplatinate (Na_2PtCl_6) was used at a maximal concentration of 1 g/L (provided by Degussa, since 2001 by Heraeus, both from Hanau, Germany) as a 10 g/L ($\sim 2 \times 10^{-2} \text{ mol/L}$) solution, diluted tenfold with saline according to international recommendations (International Platinum Association 1993, unpublished). Sensitization to Pt salt was assumed if the wheal diameter was $\geq 4 \text{ mm}$ with any concentration up to 1 g/L . A comparison of the two different Pt solutions or concentration dependence on skin reactions were not considered in this study.

Inhalative challenges with Pt salts were performed with tenfold concentrations of H_2PtCl_6 up to 10^{-2} mol/L as described earlier (Merget et al. 2009). Na_2PtCl_6 diluted in phosphate buffer at a maximal concentration of 1 g/L was used since 1993. For safety reasons and better standardization, Pt solutions were aerosolized using a DeVilbiss 646 nebulizer and an APSpro dosimeter (CareFusion) in quadrupling concentrations, as established since 2001. The application of Pt salt was the same as described for methacholine (Merget et al. 2009) with Pt salt concentrations of $0.06\text{--}1 \text{ mg/mL}$, or doses of 0.003 ng (6 fmol) to $45 \mu\text{g}$ (100 nmol) Na_2PtCl_6 . Whereas the positivity criterion was defined by body plethysmography until 2000 (doubling of specific airway resistance), the test was afterward

considered positive if (1) forced expiratory volume in 1 s (FEV₁) decreased by ≥ 20 %, or (2) specific airway resistance (sRt) doubled and increased to ≥ 2.0 kPa s after any dose.

Statistical analysis

Statistical analyses were performed using SAS/STAT and SAS/IML software, version 9.3 (SAS Institute Inc., Cary, NC, USA). Medians, lower and upper quartiles are given if not otherwise indicated to depict the distribution of continuous variables. Few subjects with airway obstruction were not submitted to methacholine testing, but were considered with hyperresponsiveness in the statistical analyses.

The outcomes of the two examinations were compared using the McNemar test or the Wilcoxon signed-rank test. Main outcome variables were symptoms (asthma, conjunctivitis, rhinitis, contact urticarial), bronchial hyperresponsiveness/airway obstruction, asthma medication and FEV₁. A *p* value < 0.05 was considered statistically significant. Potential factors influencing the main outcome parameters (age, smoking status, atopy, asthma medication and various exposure determinants [time between occurrence of symptoms and end of high exposure, duration of low exposure; time between occurrence of symptoms and start of very low or no exposure; time between end of high exposure and second exam; time between start of very low or no exposure and second exam]) were evaluated using multiple logistic (asthma symptoms, asthma medication, and bronchial hyperresponsiveness/airway obstruction) or linear regression models (FEV₁ % predicted). Confidence intervals for categorical variables were computed with GraphPad (<http://www.graphpad.com/quickcalcs/confInterval1/>). Differences between the groups of different durations of symptomatic exposures (0–<6, 6–<12, 12–<24, ≥ 24 months) were compared using the χ^2 test or the Kruskal–Wallis test.

Results

First examination

The patients were predominantly male (96 %), with a median age of 38 (range 19–61) years at the first examination (Table 1). Fifty percent of the workers were current smokers. Most of the workers were employed in precious metals refineries (86 %), with the remainder employed at catalyst plants. At the first examination, 33 % of the subjects worked in a high exposure area, and were therefore still exposed. A large number of workers had been transferred within the companies to low (20 %) or very low (39 %) exposure areas, and 8 % had left the companies.

The subjects reported a median period of 20 months (range 0.2–312 months) between the start of exposure and the occurrence of symptoms (latency), but the median time between the occurrence of symptoms and the first examination was 38 months. Prior to the first examination, 64 workers (67 %) had already been transferred from high exposure areas for a median time of 26 months, and 45 subjects (47 %) were already transferred to areas with very low or no exposure for a median time of 23 months (Table 1).

Self-reported preexisting atopy and asthma were rare in the study group (Table 2). Symptoms were frequent with dominating asthma and rhinitis. Atopy—defined as a positive SPT to environmental allergens—was documented in 41 subjects (43 %), and SPT to Pt salt was positive in 83 subjects (86 %). Mean FEV₁ was 92 % predicted, but 14 subjects (15 %) showed a FEV₁ below the 5 % percentile. Overall, 86 subjects (90 %) demonstrated airway obstruction or bronchial hyperresponsiveness. Inhalative challenges with Pt salt were positive in all but one sensitized subject, although challenges were not performed in 20 subjects (22 %) due to airways obstruction, refusal or technical reasons.

Second examination

The second examination took place 67 months (range 27–113 months) after the first examination (Table 1). There was a significant decrease in all symptoms (Table 2). Although the number of subjects with asthma also decreased, 74 subjects (77 %) still suffered from asthma (among them were four subjects who developed asthma between both examinations). The proportion of subjects taking asthma medication increased from 31 % at the first examination to 53 % at the second examination. While atopy remained unchanged, SPT_{Pt} positivity decreased from 86 % at the first examination to 52 % at the second examination. Total IgE decreased significantly ($p < 0.0001$), but the number of subjects with bronchial hyperresponsiveness or airway obstruction was similar (Table 2).

Regression models and further analyses

If the outcome parameters were related to the time period from the occurrence of new work-related symptoms to removal from high or low exposures, no significant differences were observed after stratification into short time windows (Fig. 1), or between subjects who worked in very low exposure areas within the plant ($n = 41$) and those who had left the plants (no exposure; $n = 51$) (data not shown). Logistic and linear regression models were unable to detect statistically significant effects of any of the exposure and confounding factors on outcome parameters. As power

Table 1 Characteristics of the study population ($n = 96$) at first and second examination

	1st exam		2nd exam	
Age: years [median (range)]	38 (19–61)		45 (24–67)	
Gender (male): n (%)	92 (96)		–	
Smoking status				
Never: n (%)	22 (23)		22 (23)	
Former: n (%)	26 (27)		37 (39)	
Current: n (%)	48 (50)		37 (39)	
Industrial setting				
Catalyst plant: n (%)	13 (14)		–	
Refinery: n (%)	83 (86)		–	
Exposure degree				
High: n (%)	32 (33)		2 (2)	
Low: n (%)	19 (20)		2 (2)	
Very low: n (%)	37 (39)		51 (53)	
None: n (%)	8 (8)		41 (43)	
Time periods	n		n	
Between 1st and 2nd exam: months [median (25–75 quartiles)]	– –		96	67 (27–113)
Between start of high exposure and symptoms: months [median (25–75 quartiles)]	93	20 (8–48)	94	20 (8–49)
Between occurrence of symptoms and exam: months [median (25–75 quartiles)]	93	38 (13–86)	94	129 (65–197)
Between end of high exposure and exam: months [median (25–75 quartiles)]	64	26 (10–72)	94	99 (45–157)
Between start of very low or no exposure and exam: months [median (25–75 quartiles)]	45	23 (10–63)	92	71 (37–136)
Between occurrence of symptoms and end of high exposure: months [median (25–75 quartiles)]	64	8 (2–32)	94	11 (3–31)
Between occurrence of symptoms and start of very low or no exposure: months [median (25–75 quartiles)]	45	16 (5–43)	91	24 (6–70)
Duration of high exposure: months [median (25–75 quartiles)]	–	–	96	44 (18–83)
Duration of low exposure: months [median (25–75 quartiles)]	–	–	37	47 (17–100)
Duration of very low or no exposure: months [median (25–75 quartiles)]	–	–	93	72 (41–137)

calculations yielded a chance to detect any significant effect of exposure determinants below 30 %, these data are not presented in detail.

Discussion

In this study, we report on data addressing the prognosis of occupational allergy due to Pt salts, with particular focus on asthma. Pt salt allergy offers several important features for researchers: (1) workers in large plants have regular medical check-ups and are thus often removed from exposure in a timely manner; (2) a highly specific SPT_{Pt} and the availability of an inhalative challenge with Pt salt makes misclassification unlikely; and (3) atopy is at best a modest predictor of Pt salt allergy (Heederik et al. 2016; Merget et al. 2000) and cross-reactivities to environmental allergens are unknown.

In a previous prospective cohort study in a catalyst production plant where workers were removed very early from exposure (mean 7, range 1–13 months) after sensitization was detected, a short-term follow-up up to 2 years indicated that asthma persisted in four out of 13 workers who participated in the follow-up examinations (Merget et al. 2001). However, at the time of the SPT conversion, only three subjects with follow-up examinations complained of asthma, and two out of these did not report asthma at the follow-up examination. Thus, that study demonstrated an overall favorable outcome, but the reversal of asthma symptoms was documented in only two subjects. An editorial on this study concluded that the benefits of medical surveillance to prevent OA need further research (Tarlo and Liss 2001). Although there was some improvement in asthma symptoms, the present study could not demonstrate that early removal after the occurrence of asthma symptoms resulted in better prognosis of asthma. Interestingly,

Table 2 Results of questionnaire and examinations ($n = 96$)

	History	1st exam	2nd exam	<i>p</i> value
Results of questionnaire				
Atopy in family: <i>n</i> (%)	10 (10)	–	–	–
Asthma in family: <i>n</i> (%)	11 (11)	–	–	–
Atopy: <i>n</i> (%)	6 (6)	–	–	–
Asthma prior to exposure: <i>n</i> (%)	2 (2)	–	–	–
Symptoms				
Variable shortness of breath: <i>n</i> (%)	84 (88) ^d	87 (91)	74 (77)	0.0046*
Runny nose, sneezing: <i>n</i> (%)	78 (81) ^d	80 (83)	12 (13)	<0.0001*
Itching, burning eyes: <i>n</i> (%)	57 (59) ^d	59 (61)	8 (8)	<0.0001*
Skin complaints: <i>n</i> (%)	46 (48) ^d	51 (53)	3 (3)	<0.0001*
Any: <i>n</i> (%)	90 (94) ^d	93 (97)	79 (83)	0.0005*
Asthma medication ^b : <i>n</i> (%)	–	30 (31)	51 (53)	0.0003*
Results of examination				
SPT environmental allergens (positive): <i>n</i> (%)	–	41 (43)	38 (40)	0.4669*
SPT Pt salt (positive): <i>n</i> (%)	–	83 (86)	50 (52)	<0.0001*
FEV ₁ % pred.: % [mean (min–max)]	–	92 (33–137)	89 (33–132)	0.0148 ^a
FEV ₁ <5th percentile: <i>n</i> (%)	–	14 (15)	20 (21)	0.2253*
FEV ₁ % FVC [mean (min–max)]	–	73 (24–125)	71 (32–127)	0.3503 ^a
FEV ₁ % FVC <5th percentile: <i>n</i> (%)	–	28 (29)	26 (27)	0.2207*
Total IgE: kU/L [median (25–75 quartiles)]	–	109 (32–276)	66 (30–152)	<0.0001 ^a
Bronchial hyperresponsiveness <i>n</i> (%) ^c	–	86 (90)	83 (86)	0.2059*
Inhalative challenge with Pt				
Positive tests: <i>n</i> (%)	–	75 (78)	–	–
Negative tests: <i>n</i> (%)	–	1 (1)	–	–
No test due to airways obstruction: <i>n</i> (%)	–	8 (8)	–	–
No test due to refusal or technical reasons: <i>n</i> (%)	–	12 (13)	–	–

* McNemar test

^a Wilcoxon signed-rank test^b Bronchodilators or inhaled steroids^c 4/3 subjects (1st exam/2nd exam) not tested, but 5/8 subjects (1st exam/2nd exam) with airway obstruction included^d Work-related new-onset symptoms

very early removal from exposure—not later than 6 months after the occurrence of symptoms—did not result in a better prognosis. The somewhat disparate results between this study (with a poor prognosis) and the earlier study in a catalyst production plant (with a more favorable prognosis) may be manifold. SPT_{Pt} conversion, rather than symptoms, was used as the intervention criterion for transferal in the earlier study, thus surveillance might be more beneficial when SPT_{Pt} rather than symptoms are used. The dates of the negative to positive SPT_{Pt} conversion were not recorded in this study.

An observational study design usually has several weaknesses, most importantly, a bias toward study subjects with more advanced disease. Plant physicians might not have notified subjects with less disease severity, i.e., sensitization without symptoms, but this cannot be quantified. It is noteworthy that almost all subjects reported asthma at

diagnosis. If selection due to underreporting of subjects with less severe disease occurred, the major finding that surveillance and early removal from exposure are of limited importance would still be valid in a significant number of subjects, especially those with airway symptoms. A bias toward study subjects with more advanced disease may also occur as a consequence of loss to follow-up. As follow-up examinations were initiated by the compensation boards within an official administrative procedure, relevant selection due to loss to follow-up should be limited. The number of subjects lost to follow-up was moderate (29 of 125 subjects; 23 %), and these subjects exhibited no higher disease severity (e.g., lower FEV₁) at diagnosis than those included in the study. We consider selection due to loss to follow-up as moderate at best, but this is a probable factor which may underestimate the beneficial effects of secondary prevention. A further weakness of this study design is

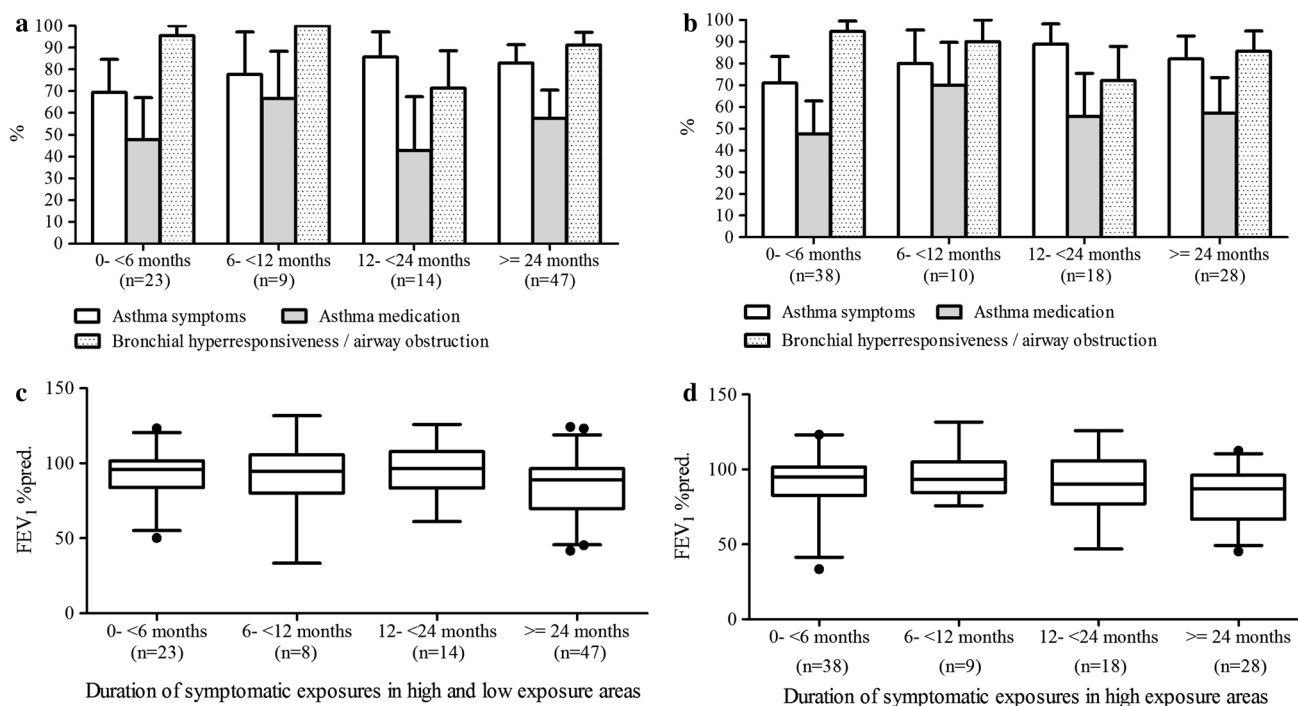


Fig. 1 Percentage (95 % CI) of subjects with asthma symptoms, asthma medication and bronchial hyperresponsiveness/airway obstruction (**a, b**) and median with 5–95 % percentile of FEV₁ (**c, d**) assigned to the duration of symptomatic exposures in high and low

exposure areas (**a, c**) or in high exposure areas (**b, d**). The different subject number in the 6–<12 months groups is due to one missing FEV₁. There were no significant differences between groups

that surveillance was not practiced in all plants on a regular basis throughout the study period and the programs were different between plants, and not standardized. Finally, ongoing exposures to irritants after removal from exposures to Pt salts, which were not assessed in this study, may have affected prognosis. We consider this unlikely as workers transferred to very low or no exposure areas did no longer complain of work-related symptoms, with few exceptions.

Prospective studies with scheduled interventions are extremely difficult to perform, and randomization is impossible due to ethical reasons. We have now developed a more concise surveillance program within one plant with mandatory early reporting of sensitization and removal from exposures after SPT_{Pt} conversion, irrespective of respiratory symptoms.

It is noteworthy that in our study several main outcomes, such as asthma symptoms and bronchial hyperresponsiveness/airway obstruction were recorded as dichotomous variables only, and were highly prevalent at all examinations which might have masked beneficial effects of interventions in case of only gradual improvements. Asthma medication was clearly confounded by the change in prescription behaviors over time. The only metric outcome FEV₁ rarely indicated severe disease at both examinations. Further attempts to assess asthma severity were not made.

Thus, surveillance may have resulted in less severe disease, but could not prevent ongoing mild asthma.

Three findings were unexpected in this study: (1) at the last examination, all but four subjects were transferred to very low or no exposure areas. This means that transfers to low exposure jobs, i.e., to jobs in the vicinity of production areas, which are quite frequent in order to avoid social disadvantages and maintain production processes by these highly qualified workers, are actually not an option for most subjects due to ongoing allergic symptoms. (2) The fact that the numbers of subjects suffering from asthma did not decrease significantly between both examinations argues for ‘a point of no return’ in the development of asthma due to Pt salts. Once the disease has been acquired, complete reversibility occurred in only a few subjects. Within this context, it is perspicuous that exposure reduction resulted in improvements, but did not affect the main outcomes in most subjects. It is noteworthy, that rhinitis, conjunctivitis and contact urticarial had a much better prognosis than asthma, although also asthma was less prevalent at the end of follow-up. (3) Medication use increased between examinations. We interpret this finding not as a progression of disease, but as a result of the introduction of anti-inflammatory drugs, especially topical steroids in the late 1980s and 1990s in Germany. On the other hand, it cannot be

excluded that medication contributed to the improvement observed in at least some of the subjects.

There is limited information on the consequences of short symptomatic exposure periods and early interventions in the literature, but in isocyanate asthma, subjects with a few months of symptomatic exposures became symptom-free, whereas asthma persisted in those with symptomatic exposure durations of longer than about 2 years (Pisati et al. 2007; Rosenberg et al. 1987). Although the cases were not described in detail, these studies provide some evidence that a tolerable time window between the occurrence of symptoms and removal from exposure may exist. The present study points to the limitations of medical surveillance of OA, although it is questionable whether the conclusions generated here on Pt salts are applicable to other allergens.

Total IgE and the frequency of SPT_{Pt} positive subjects decreased between the two examinations conducted in this study, which may be an indication of an IgE-mediated disease with an expected decrease in antibody concentrations after exposure cessation. A decrease in total IgE and SPT_{Pt} reactivity has been previously described in a smaller cohort after a shorter follow-up period once the exposure ceased (Merget et al. 1994). Although the existence of specific IgE antibodies in subjects with Pt salt allergy has not been convincingly demonstrated, an increase in the total IgE concentrations at the beginning of the occupational allergy due to Pt salts strengthens the assumption of an IgE-mediated disease (Merget et al. 2000).

One strength of the present study is that misclassification of the disease was not important due to highly specific diagnostic tools. Furthermore, tests for the assessment of outcome parameters changed little during the study period, with the exception of methacholine testing. Thus, a quantitative assessment of bronchial hyperresponsiveness was not considered. Also, the time interval between removal from exposure and the (last) examination was sufficiently long (median 67 months) to allow improvements. It is known that the most significant improvement observed in OA occurs within 2–3 years after cessation of exposure (Malo and Ghezzo 2004).

One limitation of the present study is that the exposure data of the workers cannot be provided. Whereas measurements were performed in the early 1990s in a German catalyst production plant (Merget et al. 2000), measurements were only taken occasionally in refineries, and only in high exposure areas. Recently, a comprehensive series of measurements were performed in a refinery, but the results were not provided in detail by the company. The values assigned to exposure categories given above (see ‘Methods’ section) were based on the results of these measurements and stipulated by the company itself. It is clear from the measurements acquired at the catalyst production plant that

the air concentrations of soluble Pt throughout the plants should be higher than those measured outside the plants due to contamination. As there is no indication from either the literature or from this study that these very low exposures without obvious peak exposures (below about 20 ng/m³; this is below the 25 percentile of a recent measurement series in refineries; Heederik et al. 2016) induce symptoms, transfer to such very low exposure areas within the plants should remain an option for the workers until contradictory information is available.

In summary, the overall outcome of medical surveillance as practiced in catalyst production plants and refineries in Germany during the last decades is poor with respect to asthma. There is still a need for prospective studies on the effectiveness of surveillance of workers at risk of OA due to Pt salts. The results of this study suggest that surveillance should include SPT_{Pt} as the primary tool, and that the removal from exposure should be considered irrespective of symptoms.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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