

Heavy metals and the skin: Sensitization patterns in Lithuanian metalworkers

Linauskiene Kotryna¹  | Isaksson Marlène² | Malinauskiene Laura¹ 

¹Vilnius University, Faculty of Medicine, Institute of Clinical Medicine, Clinic of Chest diseases, Immunology and Allergology, Vilnius, Lithuania

²Lund University, Skåne University Hospital, Department of Occupational and Environmental Dermatology, Malmö, Sweden

Correspondence

Linauskiene Kotryna, Vilnius University, Faculty of Medicine, Institute of Clinical Medicine, Clinic of Chest diseases, Immunology and Allergology, Santariskiu str. 2, LT-08661, Vilnius, Lithuania.
Email: kotryna.linauskiene@santa.lt

Abstract

Background: Metalworkers are exposed to many sensitizing and irritant substances. There are no published data on contact allergy in this population in the Baltic countries.

Objectives: To detect skin symptoms related to occupational exposure and to describe the reactivity pattern to the European baseline series in workers from two metal plants in Lithuania.

Methods: In this cross-sectional study 185 metalworkers (154 production workers and 31 office staff) filled an interviewer-administered questionnaire. Patch testing was performed in 135 metalworkers and office staff, as a control group.

Results: Metalworkers younger than 40 years complained statistically significantly more often of skin symptoms, especially on the hands and face, than older workers. Physician-diagnosed skin diseases were reported in 1.7% of cases. Metalworkers, working <20 years in the factory, more often had skin symptoms. Contact with chemicals at the workplace was suspected as the main factor provoking skin symptoms. Metalworkers were sensitized mainly to cobalt, and nickel was the most prevalent allergen among office staff.

Conclusion: Younger metalworkers more often had skin symptoms suspected of being work-related compared to older ones. Sensitization to cobalt was more prevalent in the metalworkers than in the control group.

KEYWORDS

cobalt, contact allergy, European baseline series, Lithuanian metalworkers, metal plant, metalworkers, nickel, office staff, patch testing

1 | INTRODUCTION

Metal allergy has for a long time been, and still is, the most frequent contact allergy among both dermatitis patients and the general population. Among the metals, nickel is the most common contact allergen with a prevalence of 10%–20% among women in the general population in Europe.¹ Skin problems related to metals are caused not primarily by hard metals in the natural environment, but are related to human activity, involving skin contact to metals and their compounds in consumer products and industrial processes. A few metals – mostly ions and compounds of nickel, chromium, and cobalt – are the major

contact allergens, causing allergic contact dermatitis (ACD) in a large proportion of the general population as well as in large occupational groups.² Occupational exposure to nickel is still of great significance for sensitization, elicitation, and maintaining and the cause of persistent hand eczema.³ Skin diseases are ~~and~~ often preventable disorders that occur in workplaces, caused by dermal exposures to irritant and sensitizing agents. Metalworking has been identified as a high-risk occupation for contact dermatitis,⁴ and currently occupational hand dermatitis in metalworkers remains poorly controlled, even after the workers change their occupation.⁵ Metal and construction workers suffering from occupational dermatitis have an increased risk of metal

allergy compared to other men with occupational dermatitis.^{6,7} The aims of the present study were to survey work-related skin diseases and to describe the sensitization patterns to the haptens of the baseline series in metalworkers, as a basis for possible preventive measures.

2 | METHODS

2.1 | Metal plants description

In plant A, situated in central Lithuania, the core activity is manufacture of nails, nets, and wire; in plant B it is the production of nails and wire. The metals that were most often handled by workers were steel, stainless steel, aluminum, and iron. In the production line, wire-drawing lubricants, soaps, oils, anti-rust agents, and degreasing solvents are mostly used. The raw materials used are composed of carbon, manganese, silico, sulfur, phosphorus, chromium, nickel, and copper. Both plants obtained raw materials from the same suppliers. The working conditions were considered similar for all metalworkers.

2.2 | Questionnaire

At the time of investigation, 185 workers (154 production workers and 31 office staff) employed at the factories voluntarily completed an interviewer-administered questionnaire providing information on their skin condition. The questionnaire consisted of signs and symptoms of skin and respiratory conditions, suspected health worsening factors suspected to impair health, demographics, and the length of time of employment. In this study only skin diseases will be discussed. The relationship among the symptoms, localization, contact with a suspected factor, and work that was performed by the study members was based on occupational dermatosis criteria.^{8,9}

2.3 | Patch testing and clinical examination

One hundred and thirty-five metalworkers and office staff, recruited as a control group in two metal plants, gave written consent to be patch tested with the European baseline series. Patch testing was offered to all personnel at work on the day the investigation was carried out. This comprised 108 of 236 (45.7%) of all the work force from plant A and 27 out of 123 (21.9%) of the workforce from plant B. From plant A, there were 63 metalworkers and 45 office staff, and from plant B, 12 and 15, respectively. Examination of each individual's skin condition was performed by an allergologist on the same day, prior to patch testing. Patch testing was performed and scored according to ESCD guidelines on site.¹⁰ The allergens and IQ Ultimate Chambers (9 × 9 mm) were provided by Chemotechnique Diagnostics (Vellinge, Sweden). Twenty microliters of liquid test solution were applied to the filter paper in the chamber, and 25 mg of test preparation in pet. was applied to the test chambers.¹⁰ The chambers were applied and left on the backs for 48 hours and the readings were

performed on day (D) 3/D4 and D7 by an allergologist trained to make patch test readings. The reactions from "+" to "+++" were classified as positive; negative, irritant, or doubtful reactions were classified as non-positive. The maximum patch test reactions from either D3/D4 or D7 were considered as an outcome. All metal workers and office staff performed their daily work during the patch testing, and the readings were done on site. Atopy was defined according to the nomenclature of the European Academy of Allergy and Clinical Immunology as the presence of allergic bronchial asthma, rhinoconjunctivitis, or atopic eczema/dermatitis.¹¹

2.4 | Statistical analysis

Statistical analysis was performed by R statistical software, version 3.5-1 (R Foundation for Statistical Computing, Vienna, Austria). The chi-squared-test or Fisher's exact test were used where appropriate (if $n \leq 5$). All results were expressed as prevalence with 95% confidence intervals, and the threshold for statistical significance was predefined as a P -value of $<.05$.

2.5 | Ethics

The study was approved by the Regional Ethics Review Board in Vilnius, Lithuania, and conducted in accordance with ethical standards specified in the Declaration of Helsinki. All patients gave written informed consent to participate in the study.

3 | RESULTS

3.1 | Questionnaire

One hundred eighty-five metal plant workers (154 metalworkers and 31 office staff) completed the interviewer-administered questionnaire to provide information about skin symptoms (eg pruritus, stinging, burning, pain, etc.) and signs (eg redness, scaling, fissures, lesions, etc.). Metalworkers <40 years complained statistically significantly more often of having skin symptoms than older ones 33/46 (71.7%) vs. 53/108 (49.1%, $P = .009$) (Figure S1). Metalworkers complained statistically significantly more often of face and hand dermatitis compared to office staff 70/154 (45.5%) vs 5/31 (16.1%, $P = .0024$) and 66/154 (42.9%) vs 4/31 (12.9%, $P = .001$), respectively (Table 1). Skin diseases diagnosed prior to this study by a physician were reported in 3/185 (1.7%) of cases, among metalworkers 1/154 (0.65%), and office staff 2/31 (6.5%). Metalworkers who had worked <20 years in the factory had skin symptoms statistically significantly more often than the metalworkers had who worked longer 70/112 (62.2%) vs. 16/42 (38.1%, $P = .007$) (Figure 2). Contact with chemicals at the workplace was statistically significantly more often suspected as the main factor provoking skin symptoms by metalworkers compared to office staff 31/154 (20.1%) vs. 9/31 (3.2%, $P = .019$). Office staff recognized

TABLE 1 Summarized questionnaire results according to dermatitis area and suspected offending cause

Complaints	Metalworkers N = 154		Administrative personnel N = 31		P-value*
	n (%)	95% CI	n (%)	95% CI	
Face dermatitis	70 (45.5)	37.8–53.3	5(16.1)	6.6–33.1	.0024
Hand dermatitis	66 (42.9)	35.3–50.7	4(12.9)	4.5–29.4	.0019
Leg dermatitis	2(1.3)	0–4.9	3(9.7)	2.56–25.6	.03
Other dermatitis	0/0	-	1(3.2)	0–17.5	
Suspected offending cause					
Chemicals	31(20.1)	14.5–27.2	1(3.2)	0–17.5	.01
Detergents	24(15.6)	10.6–22.2	9(29.0)	15.9–46.7	.04
Cold	58(37.7)	29.7–44.8	8(25.8)	13.4–43.4	.2
Heat	47/(30.5)	23.7–38.2	7(22.5)	11.1–40.1	.36
Metals	13/(8.4)	4.8–14.0	0/0	-	.13
Costume jewellery	1/(0.6)	0–3.9	2(6.5)	0.7–21.7	.07
Leather	0/0	-	0/0	-	-
Rubber	2/(1.3)	0–4.9	2(6.5)	0.7–21.7	.13

Abbreviations: CI, confidence interval; N, number of participants, n, number of positive answers.

Note: Chi-square or Fisher's exact test (if $n \leq 5$).

*Significant results $P < .05$ are shown in bold.

TABLE 2 Sex, age, and years of employment of the metal workers and office staff in the investigation during the patch testing

Sex	Male		Female		Total	
	Metalworkers	Office staff	Metalworkers	Office staff	Metalworkers	Office staff
Number	52	19	23	41	75	60
Age (years) mean (range)	42.1 (29–55)	38.3 (26–49)	50.4 (44–56)	43.6 (30–56)	44.7 (32–56)	41.9 (29–54)
Time of employment (years) mean (range)	13.7 (3.1–24.3)	12.2 (3.8–20.6)	17.6 (6.8–24.8)	14.8 (4.4–25.1)	14.8 (4.1–25.6)	13.9 (4.2–23.6)

personal hygiene products as the main culprit agent for their skin problems 9/31 (29.0%) vs. 24/154 (15.6%, $P = .04$). The results are summarized in Table 1. None of the metalworkers had an atopic history, while two men from the control group had mild atopic dermatitis.

3.2 | Skin problems among metalworkers and office staff

The general characteristics of the patch tested population are presented in Table 2. The demographics of the patch-tested study members are summarized by the MOAHLFAP Index in Table 3. The average period of employment in the plants was 14.4 ± 1.7 years. Twenty-nine of the 75 (38.6%) metalworkers and 15 out of 60 (25.0%) of the office staff complained of skin problems. The most common locations of dermatitis were the face and hands. On examination prior to the patch testing, 29 of 75 metalworkers (38.6%) and 15 of the 60 (25%) controls showed current skin signs (eg acne vulgaris, rosacea, psoriasis, and seborrheic eczema). Work related occupational dermatitis, allergic or irritant, was suspected in 11 out of 75 metalworkers; data are summarized in Table 4.

3.3 | Patch testing

Out of 135 patch-tested workers, 39 (28.9%) had at least one positive patch test reaction. Metalworkers were sensitized to cobalt (6/75) significantly more often than controls (0/60) ($P = 0.03$). Women were more often sensitized to nickel than men 12 out of 64 (18.8%) and 3 out of 71 (4.2%) ($P = .01$) with no difference between the workplaces. Among all tested individuals, the top five contact allergens were nickel sulfate (positive in 11.11%), *Myroxylon pereirae* resin (5.93%), cobalt chloride (4.44%), fragrance mix I (3.7%), and methyldibromo glutaronitrile (2.96%), but with no significant differences in age, gender, or workplace. The frequencies of positive patch test reactions to the European baseline series are summarized in Table 5.

4 | DISCUSSION

Occupational skin diseases are among the most common occupational diseases in industrial countries, although nowadays a lot of industries are moving their plants away from the European Union owing to the higher costs and strict regulations.¹² The remaining

TABLE 3 MOAHLFAP index characteristics of the tested population

MOAHLFAP characteristics	European baseline series					
	N	Positive reaction n, (%)	Metalworkers		Administrative personnel	
			N	Positive reaction n, (%)	N	Positive reaction n, (%)
Male (M)	135	71 (52.6)	75	52 (69.3)	60	19 (31.7)
Occupational (O)	135	11 (8.1)	75	11 (14.7)	60	0 (0)
Atopic dermatitis (A)	135	2 (1.5)	75	0 (0)	60	2 (3.3)
Hand (H)	135	11 (8.2)	75	10 (13.3)	60	1 (1.7)
Leg (L)	135	0 (0)	75	0 (0)	60	0 (0)
Face (F)	135	16 (11.9)	75	5 (6.7)	60	11 (18.3)
Age > 40 years (A)	135	81 (60.0)	75	48 (64.0)	60	33 (55.0)
Positivity (≥ 1 positive reaction) (P)	135	39 (28.9)	75	25 (33.3)	60	14 (23.3)

Abbreviations: N, number of tested patients, n, number of positive reactions.

	Male		Female		Total	
	n	%	n	%	n	%
Contact dermatitis	9	17.3	2	8.7	11	14.7
Atopic dermatitis	2	10.5			2	3.3
Acne	2/1	3.8/5.3	1/2	4.3/4.9	3/3	4/5
Rosacea	2/1	3.8/5.3	2/3	8.7/7.3	4/4	5.3/6.7
Seborrheic eczema	2	3.8	1/1	4.3/2.4	3/1	4/1.7
Psoriasis	1/1	1.9/5.3	1/1	4.3/2.4	2/2	2.7/3.3
Folliculitis	3/1	5.8/5.3	2/2	8.7/4.9	5/2	6.7/3.3
Mycosis fungoides	1	1.9			1	1.3
Total	20/6		9/9		29/15	

Note: Numbers in bold, metalworkers; numbers in italics, office staff.

TABLE 4 Relationship between skin disease and work in metalworkers and office staff, respectively

industrial plants are expected to have implemented better preventive measures, and create better health conditions for workers. However, this study shows that contact dermatitis is still common in metal plants.¹³

In our study, prior the survey, just 1.7% of workers had a physician-diagnosed skin disease. By contrast, based on the survey self-reported answers, the prevalence of skin problems was noticed to be rather high, and with a significant difference between metalworkers and office staff. Low numbers of physician-diagnosed cases could be explained by the ignorance of the skin symptoms by the workers. It could be a cultural feature of our society where skin problems are mostly ignored by males as being too “feminine”. High cases of contact dermatitis were noticed in the Swedish study with metalworkers and office workers having dermatitis in 54.8% and 52.6% cases, respectively.¹⁴ Young workers complained statistically significantly more often of having skin symptoms (Figures S1, and S2), and this may be explained by the fact that younger people may be more concerned about their work-related health and are more self-centered compared to older and more senior staff, who may have become used to the working conditions over the years. One more explanation why older workers in our study had less skin related complaints could be

that some other workers quit working in plants earlier due to their skin problems and could be now missed among the old workers. Resulting in false healthy study population, so called healthy workers' effect. The North Bavarian population-based study results from Germany are similar to our study, where the highest incidence rate of contact allergy was seen between the ages of 15–24 years. Interestingly, the time between starting work and the clinical presentation of contact dermatitis for metalworkers was about 4 years.¹⁵

Contact allergy to nickel is very common in the general population;^{16–19} this explains why nickel was the most prevalent allergen in women of the control group. Sensitization in the metalworkers to cobalt possibly reflects their exposure. In 2011, a review by Geier et al, addressing the presence of nickel, cobalt, and chromate in the metal working fluid, revealed that in hard metal processing, cobalt concentrations up to 300 ppm and in single cases even up to 500 ppm were documented, amounts that are possibly enough even for induction of sensitization.²⁰ The elicitation threshold in patients sensitized to cobalt is regarded to be 100–1000 ppm cobalt ions.²⁰ In damaged skin, allergic reactions could be elicited with 10 ppm of cobalt chloride (ie, 2.4 ppm cobalt).^{21,22} Geier et al recognized cobalt as an important contact allergen for metal workers and suggested that future

TABLE 5 Frequencies of positive patch test reactions to the European baseline series

No.	Substance	Conc. (%)	Metalworkers (n = 75)		Office staff (n = 60)		Male (n = 71)		Female (n = 64)	
			n/% positive	95% CI	n/% positive	95% CI	n/% positive	95% CI	n/% positive	95% CI
1.	Nickel (II)sulfate hexahydrate	5.0	15/11.11	6.75–17.6	7/9.33	4.32–18.31	8/13.33	6.65–24.43	3/4.22**	0.96–12.19
2.	Myroxylon pereiirae resin	25.0	8/5.93	2.9–11.4	4/5.33	1.7–13.33	4/6.67	2.16–16.39	5/7.04	2.68–15.81
3.	Cobalt (II)chloride hexahydrate	1.0	6/4.44	1.9–9.6	6/8*	3.4–16.7	0/0*	-	4/5.63	1.8–14.03
4.	Fragrance mix I	8.0	5/3.7	1.4–8.6	3/4	0.9–11.6	2/3.33	0.25–12.03	4/5.63	1.8–14.03
5.	Methyldibromo glutaronitrile	0.5	4/2.96	0.9–7.6	2/2.67	0.2–9.77	2/3.33	0.25–12.03	3/4.23	0.96–12.19
6.	Potassium dichromate	0.5	3/2.22	0.5–6.6	3/4	0.9–11.6	0/0	-	2/2.82	0.2–10.29
7.	Formaldehyde	2.0*	3/2.22	0.5–6.6	2/2.67	0.2–9.77	1/1.67	0–9.7	2/2.82	0.2–10.29
8.	Paraben mix	16.0	2/1.48	0.07–5.6	2/2.67	0.2–9.77	0/0	-	2/2.82	0.2–10.29
9.	Quaternium-15	1.0	2/1.48	0.07–5.6	1/1.33	0–7.87	1/1.67	0–9.7	2/2.82	0.2–10.29
10.	Budesonide	0.01	2/1.48	0.07–5.6	0/0	-	2/3.33	0.25–12.03	1/1.41	0–8.29
11.	Fragrance mix II	14.0	2/1.48	0.07–5.6	2/2.67	0.2–9.77	0/0	-	1/1.41	0–8.29
12.	Methylisothiazolinone	0.2*	2/1.48	0.07–5.6	1/1.33	0–7.87	1/1.67	0–9.7	1/1.41	0–8.29
13.	Neomycin sulfate	20.0	1/0.74	0–4.5	0/0	-	1/1.67	0–9.7	0/0	-
14.	Epoxy resin	1.0	1/0.74	0–4.5	1/1.33	0–7.87	0/0	-	1/1.41	0–8.29
15.	p-tert-Butylphenolformaldehyde resin (PTBP)	1.0	1/0.74	0–4.5	1/1.33	0–7.87	0/0	-	1/1.41	0–8.29
16.	2-Mercaptobenzothiazole (MBT)	2.0	1/0.74	0–4.5	1/1.33	0–7.87	0/0	-	1/1.41	0–8.29
17.	Sesquiterpene lactone mix	0.1	1/0.74	0–4.5	1/1.33	0–7.87	0/0	-	1/1.41	0–8.29
18.	Methylisothiazolinone+ methylchlorisothiazolinone (MI + MCI)	0.02*	1/0.74	0–4.5	0/0	-	1/1.67	0–9.7	0/0	-
19.	Hydroxyisohexyl 3-cyclohexene carboxaldehyde	5.0	1/0.74	0–4.5	1/1.33	0–7.87	0/0	-	1/1.41	0–8.29

Abbreviations: Conc, concentration; CI, confidence interval; n, number of patients.

Note: Chi-squared or Fisher's exact test (if n ≤ 5)).

Significant results (P < .05) are shown in bold.

Vehicle is pet. if not stated otherwise; * = aqua. Haptens not eliciting any positive reaction not shown in the table.

*P = .03.

**P = .01.

TABLE 6 Comparison of the prevalence of positive reactions to metals in different countries

Population	Germany EDEN study (23)		Italy EDEN study (23)		The Netherlands EDEN study (23)		Portugal EDEN study (23)		Sweden EDEN study (238)		Metalworkers Sweden (16)		Office staff Sweden (16)		Metalworkers IVDK study (10)		Lithuanian study (25)		Metal plant metalworkers		Metal plant office staff	
	General population	Positive (n), Tested % (N) (95% CI)	General population	Positive (n), Tested % (N) (95% CI)	General population	Positive (n), Tested % (N) (95% CI)	General population	Positive (n), Tested % (N) (95% CI)	General population	Positive (n), Tested % (N) (95% CI)	Metal plant workers	Positive (n), Tested % (N) (95% CI)	Metal plant workers	Positive (n), Tested % (N) (95% CI)	Patch tested patients	Positive (n), Tested % (N) (95% CI)	Patch tested patients	Positive (n), Tested % (N) (95% CI)	Metal plant workers	Positive (n), Tested % (N) (95% CI)	Metal plant office staff	Positive (n), Tested % (N) (95% CI)
Substance																						
Nickel chloride	1024 13.9 (11.8–16.0)	143 546 5*** (1.3–3.2)	87 16.4 (13.2–19.4)	500 500 500	78 15.8 (12.5–18.9)	531 531 531	98 18.5 (15.2–21.8)	518 518 518	42 8.3 (5.9–10.7)	163 11.7 (7.5–17.5)	19 21.1 (7.9–43.8)	4 5.6 (1.5–13.8)	71 29.6 (25.6–33.7)	4 9.3 (3.8–18.3)	504 29.6 (25.6–33.7)	4 5.6 (1.5–13.8)	149 29.6 (25.6–33.7)	504 29.6 (25.6–33.7)	7 9.3 (3.8–18.3)	75 9.3 (3.8–18.3)	60 13.3 (5.9–24.6)	8 13.3 (5.9–24.6)
Cobalt chloride	1024 2.3 (1.3–3.2)	546 0.9 (0.1–1.7)	500 0.9 (0.1–1.7)	500 500 500	19 3.8 (2.1–5.5)	531 531 531	13* 2.5 (1.1–3.8)	518 518 518	6** 1.1 (0.2–2.1)	163 2.5 (0.7–6.3)	19 0 ^y -	1 1.4 (0–7.4)	73 8.7 (6.4–11.5)	1 8 (2.9–16.6)	504 8.7 (6.4–11.5)	1 1.4 (0–7.4)	44 8.7 (6.4–11.5)	504 8.7 (6.4–11.5)	6 8 (2.9–16.6)	75 8 (2.9–16.6)	60 0 ^y -	0 ^y -
Potassium dichromate	1024 1.1 (0.5–1.8)	546 0.4 (0–0.9)	500 0.4 (0–0.9)	500 500 500	2 [§] 0.4 (0–0.9)	531 531 531	7 1.8 (0.4–2.3)	518 518 518	1 [§] 0.2 (0–0.7)	163 2.5 (0.7–6.3)	19 5.3 (0–26.4)	1 1.4 (0–7.4)	73 6.6 (4.5–9.1)	1 4 (0.8–11.3)	504 6.6 (4.5–9.1)	1 1.4 (0–7.4)	33 6.6 (4.5–9.1)	504 6.6 (4.5–9.1)	75 4 (0.8–11.3)	60 4 (0.8–11.3)	0 -	0 -

Abbreviations: CI, confidence interval; IVDK, Information Network of Departments of Dermatology; N, number of tested patients; n, number of positive reactions.

Note: Chi-squared or Fisher's exact test (if $n \leq 5$).Significant results compared to our study results ($P < .05$) are shown in bold.^y $P = .03$.^{*} $P = .02$.^{**} $P = .001$.^{***} $P = .0001$.^{****} $P = .003$.[§] $P = .007$.[§] $P = .01$.

investigations on cobalt allergies among metalworkers should describe in detail the kind of metal the patient handles.²² In our study we know that nets, wire, and nails do not contain measurable amounts of cobalt, suggesting that the contact with cobalt is from other work appliances or instruments. We also know that producing these items usually does not involve extensive skin contact with metal-working fluids necessary for cutting and grinding of metals. Most of the workers did not use gloves at all or used white cotton gloves, which after the shift were black and greasy, leaving their hands dirty. The type of gloves that were used at the time of investigation did not protect hands from contact with oils and lubricants, which are possible contact irritants and allergens. Hence, it can be speculated that workers without protective gloves have constant skin irritation and this increases penetration of the cobalt into the skin and induces sensitization.

The Information Network of Departments of Dermatology (IVDK)¹³ retrospectively analyzed data from 2007–2016 where 3411 patients were patch tested, including 83 metalworkers. A Swedish study on occupational dermatoses in a metalworking plant producing engines and drivelines for the automotive industry was performed in 1999–2000. In this study, 164 metal workers and 19 office staff were interviewed and patch tested. The prevalence of contact allergy to nickel sulfate, cobalt chloride, and potassium dichromate among metalworkers from Lithuania, Sweden,¹⁴ and in the IVDK study¹³ was comparable (Table 4). Nickel is restricted under Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) regulations, which controls nickel release from items that have prolonged contact with the skin. Unfortunately, most of the metalworkers work producing items are not intended to be in prolonged skin contact, so the directive does not impose any regulation in this setting. Denmark, Germany, and Sweden introduced this legislation in 1990 and 1991, which has been the basis for the European Union Nickel Directive.^{13,23}

We compared our data with the European general population, namely, the EDEN study participants, and found a significant difference in cobalt chloride sensitization between metalworkers and the EDEN study participants from Sweden, Portugal, Italy, and Germany.²⁴ Furthermore, sensitization to potassium dichromate differed statistically significantly between metalworkers and the EDEN study's participants from Sweden, the Netherlands, and Italy. The data analysis with significance levels is shown in Table 6. A similar situation was present when patch testing the general population in the EDEN study. This indicates that sensitization to cobalt chloride and potassium dichromate is, possibly, occupation related.

The comparison in Table 6 shows that patch testing patients with suspected contact dermatitis produces higher positivity rates²⁵ compared to testing the general population.

One weakness of this study is that workplace materials were not tested and, consequently, we might have missed contact sensitization to other allergens than the ones in the European baseline series. Moreover, as another limitation of this study, not all the workers answered the questionnaire and not everybody agreed to be patch

tested. Therefore, it could be that persons already having skin problems were more prone to part this study. We could not assess the influence of atopy because of the small size of our tested population.

In conclusion, younger metalworkers reported skin symptoms more frequently than older metalworkers. Sensitization to cobalt was more prevalent than in the general population or among dermatitis patients, possibly reflecting increased occupational exposure. Education of the workers regarding skin safety and protective equipment usage is still required since it seems that it is still not a daily routine.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Isaksson Marlène: Methodology; supervision; writing-review and editing. **Laura Malinauskiene:** Conceptualization; investigation; methodology; project administration; supervision; validation; writing-review and editing. **Linauskiene Kotryna:** Conceptualization; data curation; formal analysis; investigation; methodology; project administration; validation; visualization; writing-original draft.

ORCID

Linauskiene Kotryna  <https://orcid.org/0000-0002-4693-0436>

Malinauskiene Laura  <https://orcid.org/0000-0001-5834-5915>

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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Heavy metals and the skin: sensitization patterns in Lithuanian metalworkers

Linauskiene Kotryna*¹, Isaksson Marlène*², Malinauskiene Laura*¹

¹Vilnius University, Faculty of Medicine, Institute of Clinical Medicine, Clinic of Chest diseases, Immunology and Allergology, Vilnius, Lithuania.

²Lund University, Skåne University Hospital, Department of Occupational and Environmental Dermatology, Malmö, Sweden.

Corresponding author: Kotryna Linauskiene

Vilnius University, Faculty of Medicine, Institute of Clinical Medicine,
Clinic of Chest diseases, Immunology and Allergology, Santariskiu str. 2,
LT-08661, Vilnius, Lithuania.

Tel. +37069771335; e-mail: kotryna.linauskiene@santa.lt

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Keywords: contact allergy, metalworkers, office staff, metal plant, Lithuanian metalworkers, patch testing, cobalt, nickel, European baseline series.

SUMMARY

Background: Metalworkers are exposed to many sensitizing and irritant substances. There are no published data on contact allergy in this population in the Baltic countries.

Objective: To detect skin symptoms related to occupational exposure and to describe the reactivity pattern to the European baseline series in workers from two metal plants in Lithuania.

Methods: In this cross-sectional study 185 metalworkers (154 production workers and 31 office staff) filled an interviewer-administered questionnaire. Patch testing was performed in 135 metalworkers and office staff, as a control group.

Results: Metalworkers younger than 40 years statistically significantly more often complained of skin symptoms especially on hands and face than older ones. Physician-diagnosed skin diseases were reported in 1.7% of cases. Metalworkers, working <20 years in the factory, more often had skin symptoms. Contact with chemicals at the workplace was suspected as main factors provoking skin symptoms. Metalworkers were sensitized mainly to cobalt chloride, and nickel was the most prevalent allergen among the office staff.

Conclusion: Younger metalworkers more often had skin symptoms suspected of being work-related compared to older ones. Sensitization to cobalt was more prevalent in the metalworkers than in controls.

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57 1. Introduction

58 Metal allergy has for a long time been, and is still, the most frequent contact allergy among both
59 dermatitis patients and the general population. Amongst the metals nickel is the most common
60 contact allergen with a prevalence of 10-20 % among women in the general population in Europe
61 (1). Skin problems related to metals are caused not primarily by hard metals in the natural
62 environment but are related to human activity, involving skin contact to metallic metals and their
63 compounds in consumer products and industrial processes. A few metals – mostly ions and
64 compounds of nickel (Ni), chromium (Cr), and cobalt (Co) -- are the major contact allergens,
65 causing allergic contact dermatitis (ACD) in a large proportion of the general population as well
66 as in large occupational groups (2). Occupational exposure to Ni is still of great importance for
67 sensitization, elicitation and maintaining hand eczema (3). Skin diseases are important and often
68 preventable diseases occurring in workplaces with dermal exposures to irritant and sensitizing
69 agents. Metalworking has been identified as a high-risk occupation for contact dermatitis, (4)and
70 currently the prognosis of occupational hand dermatitis in metalworkers remain poorly
71 controlled even after they change their occupation (5). Metal and construction workers suffering
72 from occupational dermatitis have an increased risk of metal allergy compared to other men with
73 occupational dermatitis (6,7). The aims of the study were a survey of work-related skin diseases
74 and description of the sensitization patterns to the haptens of the baseline series in metalworkers
75 as a basis for possible preventive measures.

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77 2. Methods and materials

78 2.1 Metal plants description

79 The core activity in a plant A, situated in central Lithuania, is manufacture of nail, net, and wire,
80 and in a plant B the production of nails and wire. The metals that were most often handled by
81 workers were steel, stainless steel, aluminum, and iron. In the production line mostly wire-
82 drawing lubricants, soaps, oils, anti-rust agents, and degreasing solvents are used. The raw

materials used are composed of C, Mn, Si, S, P, Cr, Ni, and Cu. Both plants gained raw material from the same suppliers. The working conditions were considered similar in all metalworkers.

2.2 Questionnaire

At the time of investigation 185 workers (154 production workers and 31 office staff) employed at the factories voluntarily filled an interviewer-administered questionnaire providing information on their skin condition. The questionnaire consisted of signs and symptoms of skin and respiratory conditions, suspected health worsening factors, demographics and time of employment. In this study only skin diseases will be discussed. The relationship between the symptoms, localization, contact with suspected factor and work that was performed by the study members was based on occupational dermatosis criteria (8,9).

2.3 Patch testing and clinical examination

One hundred and thirty-five metalworkers and office staff, as a control group, in two metal plants, gave written consent to be patch tested with the European baseline series. Patch testing was offered to all personnel present at work on the day when investigation was carried out. This comprised 45.7% (108/236) of all the work force from plant A and 21.9% (27/123) from plant B. From plant A there were 63 metalworkers and 45 office staff and from plant B 12 and 15, respectively. The examination of each individual's skin condition was performed by an allergologist on the same day as the patch testing but prior to it. Patch testing was performed and scored according to ESCD guidelines on site (10). The allergens and IQ Ultimate Chambers (9×9mm) were provided by Chemotechnique Diagnostics (Vellinge, Sweden). Twenty microliters of liquid test solution were applied to the filter paper in the chamber, and 25 mg of test preparation in pet. was applied to the test chambers (10). The chambers were applied and left on the backs for 48 hours (h) and the readings were performed on day (D) 3/D4 and D7 by an allergologist trained to perform patch test readings. The reactions from “+” to “+++” were classified as positive, and negative, irritant, or doubtful reactions were classified as non-positive. The maximum patch test reactions from either D3/D4 or D7 were considered as an outcome. All metal workers and office staff were performing their daily work during the patch testing, and the reading was done on site. Atopy was defined according to the nomenclature of the European Academy of Allergy and Clinical Immunology as the presence of allergic bronchial asthma, rhinoconjunctivitis, or atopic eczema/dermatitis (11).

2.4 Statistical analysis and Ethics

Statistical analysis was performed by R statistical software, version 3.5-1. The χ^2 -test or Fisher's exact test was used where appropriate (if $n \leq 5$). All results were expressed as prevalence with 95% confidence intervals, and the threshold for statistical significance was predefined as a P -value of $<.05$.

The study was approved by the Regional Ethics Review Board in Vilnius, Lithuania, and conducted in accordance with ethical standards specified in the Declaration of Helsinki. All patients gave informed written consent to participate in the study.

3. Results

3.1 Questionnaire

One hundred eighty-five metal plant workers (154 metalworkers and 31 from administrative personnel) completed the interviewer-administered questionnaire to provide information about skin symptoms (e.g. pruritus, stinging, burning or pain, etc.) and signs (e.g. redness, scaling, fissures, lesions, etc.). Metalworkers younger than 40 years, statistically significantly more often complained of having skin symptoms than older ones (71.73% (33/46) vs. 49.07% (53/108), $P=.009$) (*Fig.1*). Metalworkers statistically significantly more often had complaints of face and hand dermatitis compared to administrative personnel (45.45% (70/154) vs 16.13% (5/31) $P=.0024$ and 42.86% (66/154) vs 12.9% (4/31) $P=.001$), respectively (Table 1). Skin diseases diagnosed prior to this study by a physician were reported in 1.7% (3/185) of cases, among metalworkers 0.65% (1/154), and office staff 6.45% (2/31). Metalworkers, working less than 20 years in the factory, statistically significantly more often had skin symptoms compared with the metalworkers working longer (62.2% (70/112) vs. 38.09% (16/42), $P=.007$) (*Fig.2*). Contact with chemicals at the workplace was statistically significantly more often suspected as the main factor provoking skin symptoms by metalworkers compared to office staff (20.13% (31/154) vs. 3.22% (9/31) $P=.019$). Office staff recognized personal hygiene products as the main culprit agent for their skin problems 29.03% (9/31) vs. 15.58% (24/154) $P=.04$. The results are summarized in Table 1. None of the metalworkers had an atopic history, while two men from the control group had mild an atopic dermatitis.

3.2 Skin problems among metalworkers and office staff

The general characteristics of the patch tested population are presented in Table 2. The demographics of the patch -tested study members are summarized by the MOAHLFAP index in Table 3. The average period of employment in the plants was 14.4 ± 1.7 years. Thirty-eight per cent (29/75) of metalworkers and 25.0% (15/60) of the office staff complained of skin problems. The most common locations of dermatitis were face and hands. On examination prior to the patch testing 29 of the 75 metalworkers (38.6%) and 15 of the 60 (25%) controls showed current skin signs (e.g., acne vulgaris, rosacea, psoriasis and seborrheic eczema). Work related occupational dermatitis, allergic or irritant, was suspected in 11 out of 75 metalworkers data is summarized in Table 4.

3.3 Patch testing

Out of 135 patch tested workers, 39 (28.9%) had at least one positive patch test reaction. Metalworkers were sensitized to cobalt chloride (6/75) significantly more often than controls (0/60) ($p=0.03$). Women were more often sensitized to nickel sulfate than men (18.75% (12/64) and 4.22% (3/71) ($P=.01$)) with no difference between the workplaces. Among all tested individuals the top 5 contact allergens were nickel sulfate (positive in 11.11%), *Myroxylon perei* resin (5.93%), cobalt chloride (4.44%), fragrance mix I (3.7%) and methyldibromoglutaronitrile (2.96%), but with no significant difference between age, gender or workplace. The frequencies of positive patch test reactions to the European baseline series are summarized in Table 5.

4. Discussion

Occupational skin diseases are among the most common occupational diseases in industrial countries, although nowadays a lot of industries are moving their plants away from the EU owing to the higher costs and strict regulations (12). Remaining industrial plants are expected to have implemented better preventive measures, and better health conditions are created for workers. However, this study shows that contact dermatitis is still common in the metal plants (13). In our study prior the survey just 1.7% of workers had physician-diagnosed skin disease. By contrast, based on the survey self-reported answers, the prevalence of skin problems was noticed to be rather high and with significant difference between metalworkers and office staff. Low

173 numbers of physician-diagnosed cases could be explained by the ignorance of the skin symptoms
174 by the workers. It could be cultural feature of our society where skin problems by males are
175 mostly ignored as too “feminine”. High numbers of CD were noticed in the Swedish study with
176 metalworkers and staff clerks having dermatitis in 54.8% and 52.6% cases, respectively (14).
177 Young workers statistically significantly more often complained of having skin symptoms (Fig.
178 1, 2), and this may be explained by the fact that younger age people may be more concerned of
179 their work-related health and are more self-centered compared to older and more senior staff,
180 who are usually used to the working conditions over the years. The healthy worker’s effect- the
181 ones who left work early due to skin problems a long time ago are missed among the old
182 workers, this could be one more explanation to why the old ones had fewer complaints. The
183 Northern Bavarian Germany population-based studies results are similar to our study where the
184 highest incidence rate of contact allergy was seen at the young age - between 15-24 years.
185 Interestingly, the time between start of job and the clinical presentation of CD for metalworkers
186 was about 4 years (15).

187 Contact allergy to nickel is very common in the general population (16-19); this explains
188 nickel being the most prevalent allergen in women of the control group. Sensitization in the
189 metalworkers to cobalt possibly reflects their exposure. In 2011, a review by Geier et al,
190 addressing the presence of nickel, cobalt, and chromate in the metal working fluid (MWF),
191 revealed that in hard metal processing, cobalt concentrations up to 300 ppm and in single cases
192 even up to 500 ppm were documented, amounts that are possibly enough even for induction of
193 sensitization (20). The elicitation threshold in patients sensitized to cobalt is regarded to be 100-
194 1000 ppm cobalt ions (20). In damaged skin allergic reactions could be elicited with 10 ppm of
195 cobalt chloride (ie, 2.4 ppm cobalt) (21,22). Geier et al recognized cobalt as an important contact
196 allergen for metal workers and suggested that future investigations on cobalt allergies among
197 metalworkers should describe in detail the kind of metal the patient handles (22). In our study we
198 know that net, wire, and nails do not contain measurable amounts of cobalt, suggesting that the
199 contact with cobalt is from other work appliances or instruments. We also know that producing
200 these items usually does not involve extensive skin contact with metal working fluids, necessary
201 for cutting and grinding of metals. Most of the workers did not use gloves at all or used white
202 cotton gloves, which after the work shift were black and greasy, leaving their hands dirty. The
203 type of gloves that were used at the time of investigation did not protect hands from contact with

oils and lubricants, which are possible contact irritants and allergens. Hence, it can be speculated that workers without protective gloves have constant skin irritation and this increases penetration of the cobalt into the skin and induce sensitization.

A IVDK study (13) retrospectively analyzed the data of 2007-2016, where 3411 patients were patch tested, among those 83 metalworkers. A Swedish study on occupational dermatoses in a metalworking plant producing engines and drivelines for the automotive industry was performed in 1999-2000. In this study, 164 metal workers and 19 office staff were interviewed and patch tested. The prevalence of contact allergy to nickel sulfate, cobalt chloride, and potassium dichromate among metalworkers from Lithuania, Sweden (14), and in the IVDK study (13) members was comparable (Table 4). Nickel is restricted under REACH, which regulates nickel release from items that have prolonged contact with the skin. Unfortunately, most of the metalworker's work producing items are not intended to be in prolonged skin contact, so the directive does not impose any regulation in this setting. Denmark, Germany, and Sweden introduced this legislation in 1990 and 1991, which has been the basis for the EU Nickel Directive (13, 23).

We compared our data with the European general population, namely, the EDEN study participants, and found a significant difference in cobalt chloride sensitization between metalworkers and the EDEN study participants from Sweden, Portugal, Italy, and Germany (24). Furthermore, sensitization to potassium dichromate statistically significantly differed between metalworkers and the EDEN study's participants from Sweden, The Netherlands, and Italy. The data analysis with significance levels is shown in Table 6. A similar situation was present when patch testing the general population in the EDEN study. This indicates that sensitization to cobalt chloride and potassium dichromate possibly is occupation- related.

The comparison in table 6 shows that patch testing patients with suspected CD produces higher positivity rates (25) compared to testing the general population.

One weakness of this study is that workplace materials were not tested, and consequently we might have missed contact sensitization to other allergens than the ones in the European baseline series. Moreover, as a limitation of this study, not all the workers answered the questionnaire and not everybody agreed to be patch tested. Thereby, it could be that persons already having skin

problems were more prone to enter this study. We could not assess influence of atopy due to the small size of our tested population.

In conclusion, younger metalworkers reported skin symptoms more frequently than older metalworkers. Sensitization to cobalt was more prevalent than in the general population or among dermatitis patients, possibly reflecting increased occupational exposure. Education of the workers regarding skin safety and protective equipment is still required since it is not self-evident.

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359 Table 1. Summarized questionnaire results according to dermatitis area and suspected offending
 360 cause.

Complaints	Metalworkers N=154		Administrative personnel N=31		7-value
	n, (%)	95% CI	n, (%)	95% CI	
Face dermatitis	70 (45.5)	37.8-53.3	5(16.1)	6.6-33.1	.0024
Hand dermatitis	66 (42.9)	35.3-50.7	4(12.9)	4.5-29.4	.0019
Leg dermatitis	2(1.3)	0-4.9	3(9.7)	2.56-25.6	.03
Other dermatitis	0/0	-	1(3.2)	0-17.5	
Suspected offending cause					
Chemicals	31(20.1)	14.5-27.2	1(3.2)	0-17.5	.01
Detergents	24(15.6)	10.6-22.2	9(29.0)	15.9-46.7	.04
Cold	58(37.7))	29.7-44.8	8(25.8)	13.4-43.4	.2
Heat	47/(30.5)	23.7-38.2	7(22.5)	11.1-40.1	.36
Metals	13/(8.4)	4.8-14.0	0/0	-	.13
Costume jewellery	1/(0.6)	0-3.9	2(6.5)%	0,7-21.7	.07
Leather	0/0	-	0/0	-	-
Rubber	2/(1.3)	0-4.9	2(6.5)%	0.7-21.7	.13

361 N – number of participants, n – number of positive answers

362 CI, confidence interval.

363 Chi-square or Fisher's exact test (if $n \leq 5$).

364 Significant results ($P < .05$) are shown in bold.

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Table 2. Sex, age, and employment time of the metal workers and the office staff in the investigation during the patch testing

Sex	Male		Female		Total	
	Metalworkers	Office staff	Metalworkers	Office staff	Metalworkers	Office staff
Number	52	19	23	41	75	60
Mean age, years (range)	42.1 (29-55)	38.3 (26 - 49)	50.4 (44-56)	43.6 (30-56)	44.7 (32-56)	41.9 (29-54)
Mean time of employment, years (range)	13.7 (3.1-24.3)	12.2 (3.8-20.6)	17.6 (6.8-24.8)	14.8 (4.4-25.1)	14.8 (4.1-25.6)	13.9 (4.2-23.6)

Table 3. MOAHLFAP index characteristics of the tested population.

Characteristics	European baseline series					
			Metalworkers		Administrative personnel	
	N	Positive reaction n, (%)	N	Positive reaction n, (%)	N	Positive reaction n, (%)
Male (M)	135	71 (52.6)	75	52 (69.3)	60	19 (31.7)
Occupational (O)	135	11/135 (8.1)	75	11 (14.7)	60	0 (0)
Atopic dermatitis (A)	135	2/135 (1.5)	75	0 (0)	60	2 (3.3)
Hand (H)	135	11 (8.2)	75	10 (13.3)	60	1 (1.7)
Leg (L)	135	0 (0)	75	0 (0)	60	0 (0)
Face (F)	135	16 (11.9)	75	5 (6.7)	60	11 (18.3)
Age>40 years (A)	135	81 (60.0)	75	48 (64.0)	60	33 (55.0)
Positivity (≥ 1 positive reaction) (P)	135	39 (28.9)	75	25 (33.3)	60	14 (23.3)

N – number of tested patients, n – number of positive reactions.

Table 4.

Relationship between skin disease and work in metalworkers and office staff, respectively.

	Male		Female		Total	
	n	%	n	%	n	%
Contact dermatitis	9	17.3	2	8.7	11	14.7
Atopic dermatitis	2	<i>10.5</i>			2	<i>3.3</i>
Acne	2/1	3.8/5.3	1/2	4.3/4.9	3/3	4/5
Rosacea	2/1	3.8/5.3	2/3	8.7/7.3	4/4	5.3/6.7
Seborrheic eczema	2	3.8	1/1	4.3/2.4	3/1	4/1.7
Psoriasis	1/1	1.9/5.3	1/1	4.3/2.4	2/2	2.7/3.3
Folliculitis	3/1	5.8/5.3	2/2	8.7/4.9	5/2	6.7/3.3
Mycosis fungoides	1	1.9			1	1.3
Total	20/6		9/9		29/15	

Figures in bold – metalworkers. Figures in italics – office staff.

No.	Substance	Conc. (%)	Total n=135			Metalworkers (n=75)		Administrative personnel (n=60)		Male (n= 71)		Female (n= 64)	
			n positive	% positive	95% CI	n/% positive	(95% CI)	n/% positive	(95% CI)	n/% positive	(95% CI)	n/% positive	(65% CI)
1.	Nickel (II)sulfate hexyhydrate	5.0	15	11.11	6.75 - 17.6	7/9.33	4.32- 18.31	8/13.33	6.65- 24.43	3/4.22**	0.96- 12.19	12/18.75**	10.9- 30.13
2.	<i>Myroxylon pereirae</i> resin	25.0	8	5.93	2.9- 11.4	4/5.33	1.7- 13.33	4/6.67	2.16- 16.39	5/7.04	2.68- 15.81	3/4.69	1.08- 13.43
3.	Cobalt (II)chloride hexahydrate	1.0	6	4.44	1.9- 9.6	6/8*	3.4- 16.7	0/0*	-	4/5.63	1.8- 14.03	2/3.13	0.2- 11.33
4.	Fragrance mix I	8.0	5	3.7	1.4- 8.6	3/4	0.9- 11.6	2/3.33	0.25- 12.03	4/5.63	1.8- 14.03	1/1.56	0- 9.14
5.	Methyldibromo glutaronitrile	0.5	4	2.96	0.9- 7.6	2/2.67	0.2- 9.77	2/3.33	0.25- 12.03	3/4.23	0.96- 12.19	1/1.56	0- 9.14
6.	Potassium dichromate	0.5	3	2.22	0.5- 6.6	3/4	0.9- 11.6	0/0	-	2/2.82	0.2- 10.29	1/1.56	0- 9.14
7.	Formaldehyde	2.0*	3	2.22	0.5- 6.6	2/2.67	0.2- 9.77	1/1.67	0-9.7	2/2.82	0.2- 10.29	1/1.56	0- 9.14
8.	Paraben mix	16.0	2	1.48	0.07 -5.6	2/2.67	0.2- 9.77	0/0	-	2/2.82	0.2- 10.29	0/0	-
9.	Quaternium-15	1.0	2	1.48	0.07 -5.6	1/1.33	0- 7.87	1/1.67	0-9.7	2/2.82	0.2- 10.29	0/0	-
10.	Budesonide	0.01	2	1.48	0.07 -5.6	0/0	-	2/3.33	0.25- 12.03	1/1.41	0- 8.29	1/1.56	0- 9.14

11.	Fragrance mix II	14.0	2	1.48	0.07 -5.6	2/2.67	0.2- 9.77	0/0	-	1/1.41	0- 8.29	1/1.56	0- 9.14
12.	Methylisothiazolinone	0.2*	2	1.48	0.07 -5.6	1/1.33	0- 7.87	1/1.67	0-9.7	1/1.41	0- 8.29	1/1.56	0- 9.14
13.	Neomycin sulfate	20.0	1	0.74	0-4.5	0/0	-	1/1.67	0-9.7	0/0	-	1/1.56	0- 9.14
14.	Epoxy resin	1.0	1	0.74	0-4.5	1/1.33	0- 7.87	0/0	-	1/1.41	0- 8.29	0/0	-
15.	<i>p</i> -tert- Butylphenolformaldehyde resin (PTBP)	1.0	1	0.74	0-4.5	1/1.33	0- 7.87	0/0	-	1/1.41	0- 8.29	0/0	-
16.	2-Mercaptobenzothiazole (MBT)	2.0	1	0.74	0-4.5	1/1.33	0- 7.87	0/0	-	1/1.41	0- 8.29	0/0	-
17.	Sesquiterpene lactone mix	0.1	1	0.74	0-4.5	1/1.33	0- 7.87	0/0	-	1/1.41	0- 8.29	0/0	-
18.	Methylisothiazolinone+methyl chloroisothiazolinone (MI+MCI)	0.02*	1	0.74	0-4.5	0/0	-	1/1.67	0-9.7	0/0	-	1/1.56	0- 9.14
19.	Hydroxyisohexyl 3- cyclohexene carboxaldehyde	5.0	1	0.74	0-4.5	1/1.33	0- 7.87	0/0	-	1/1.41	0- 8.29	0/0	-

385 Conc, concentration; CI, confidence interval; n, number of patients.

386 Chi-square or Fisher's exact test (if n≤5).

387 Significant results ($P<.05$) are shown in bold.

388 * $P=.03$

389 ** $P=.01$

390 Vehicle is petrolatum if not stated otherwise; *= aqua.

391 Negative resulted haptens are not shown in the table.

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407 Table 6. Comparison of the prevalence of positive reactions to metals in different countries.

[illegible]

		(95% CI)		(95% CI)		(95% CI)		(95% CI)		(95% CI)		(95% CI)		(95% CI)		(95% CI)		(95% CI)		(95% CI)		% (95% CI)
Nickel chloride	102 4	143 13.9 (11.8- 16.0)	546	87 16.4 (13.2- 19.4)	500	78 15.8 (12.5- 18.9)	531	98 18.5 (15.2- 21.8)	518	42 8.3 (5.9- 10.7)	163	19 11.7 (7.5- 17.5)	19	4 21.1 (7.9- 43.8)	71	4 5.6 (1.5- 13.8)	504	149 29.6 (25.6- 33.7)	75	7 9.3 (3.8- 18.3)	60	8 13.3 (5.9- 24.6)
Cobalt chloride	102 4	24**** 2.3 (1.3-3.2)	546	5**** 0.9 (0.1-1.7)	500	19 3.8 (2.1- 5.5)	531	13* 2.5 (1.1- 3.8)	518	6** 1.1 (0.2- 2.1)	163	4 2.5 (0.7- 6.3)	19	0[‡] -	73	1 1.4 (0-7.4)	504	44 8.7 (6.4- 11.5)	75	6 8 (2.9- 16.6)	60	0[‡] -
Potassium dichromate	102 4	12 1.1 (0.5-1.8)	546	2^{&} 0.4 (0-0.9)	500	2^{&} 0.4 (0- 0.9)	531	7 1.8 (0.4- 2.3)	518	1[§] 0.2 (0- 0.7)	163	4 2.5 (0.7- 6.3)	19	1 5.3 (0-26.4)	73	1 1.4 (0-7.4)	504	33 6.6 (4.5- 9.1)	75	3^{§&} 4 (0.8- 11.3)	60	0 -

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N – number of tested patients, n – number of positive reactions

409

CI, confidence interval.

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Chi-square or Fisher’s exact test (if n≤5).

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Significant results compared to our study results (*P*<.05) are shown in bold.

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[‡]*P*=.03

413

^{*}*P*=.02

414

^{**}*P*=.001

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^{***}*P*=.0001

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^{****}*P*=.003

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[§]*P*=.007

418

[&]*P*=.01

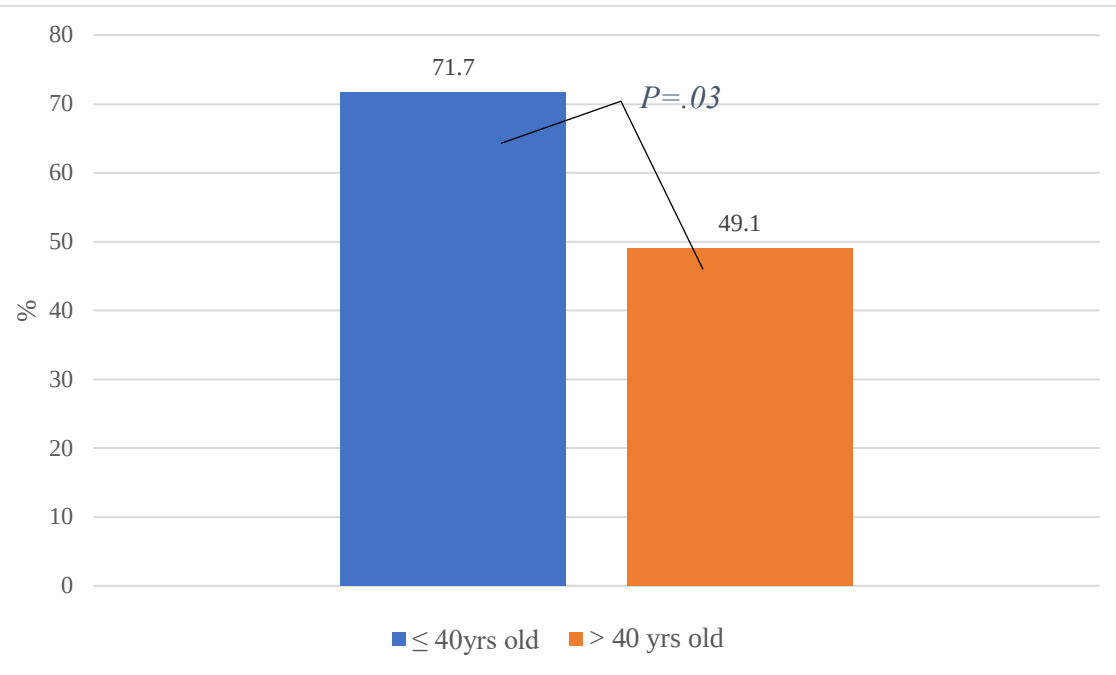
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Online supplemental Fig. 1 Skin symptom complaints according to the metalworkers’ age.

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