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Indium and iridium: Two rare metals with a high rate of contact sensitization

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Abstract

Background: Humans are exposed to a variety of metals on a daily basis, and nickel is the most frequent contact allergen. Little is known about the frequency of sensitization to indium and iridium.

Objectives: Study the prevalence of indium and iridium sensitization and evaluate the optimal patch test conditions.

Methods: A total of 364 patients were patch tested at the allergy unit of the University Hospital of Basel. Pure metals, metal chlorides, and metal sulfates were applied in petrolatum or water in Inert Quadrate (IQ) test chambers for 2 days and read twice at day (D) 2, and between D4 and D7.

Results: Eleven patients reacted to indium salts (3.0%), 13 to iridium salts (3.6%), and one reacted to both salts. None of the patients reacted to pure metals. Nineteen of the 23 patients who reacted either to indium or iridium showed concomitant positive reactions to other metals, mainly nickel and palladium.

Conclusion: This retrospective clinical study provides insight into the prevalence and test conditions of two rarely tested metal allergens in a large patient cohort. A considerable number of indium- or iridium-positive subjects had co-sensitization to other metals.

KEYWORDS

allergic contact dermatitis, indium, iridium, metal allergy, metal hypersensitivity, patch test

1 | INTRODUCTION

Humans are often exposed to a variety of metals, which are commonly present in the environment, for example, in jewelry, medical devices, and implants, as well as food, cosmetics, drugs, and consumer electronics, and in occupational settings. Nickel, palladium, cobalt, and chromium are well-known sensitizing metals that can induce allergic contact dermatitis or stomatitis. Less is known about other rare metals such as indium and iridium, which are increasingly present in implants, electronic devices, and jewelry.¹

Ferdinand Reich and Hieronymus Theodor Richter discovered indium in 1863. They named it after the characteristic atomic spectrum of two indigo blue lines.² The first large-scale application of indium was during World War II, where it was used as a coating for

bearings in high-performance aircraft engines. Afterwards, production increased gradually as new uses were found in solders, fusible alloys, and electronics. From the 1980s, indium gained much interest for the production of flat and touch screens.

Today this metal is used in nuclear medicine as tracer, as catalyst in dentistry to increase the hardness of certain alloys,^{3,4} and is also found in jewelry.⁵ Even though the estimated value of refined indium consumed domestically in 2018 in the United States was about \$53 million,³ there are only six publications regarding the prevalence of sensitizations to this metal, with proportions varying between 0% and 4%.^{6–11} Test preparations reported in the literature are the following: indium 1% pet.; indium (III) chloride 1%, 3.11%, and 10% aq.; and indium sulfate 1%, 3.16%, and 10% aq.^{1,9}

Iridium was discovered by the English chemist Smithson Tennant in 1803. Its name derives from the Greek word iris ("rainbow"), referring to the various colors of its compounds.¹² It is a very rare, very hard, and brittle metal, and one of the densest terrestrial substances. Iridium is used mainly in platinum alloys, which are readily workable, and much harder and resistant to chemical attack than pure platinum. Such alloys are used for jewelry, pen points, as in endovascular grafts, and in cathodes of x-ray sources. Furthermore, iridium is found in trace amounts in gold- and mercury-containing dental alloys.^{1,13,14} Test preparations reported in the literature are the following: ammonium hexachloroiridate 0.01%, 0.032%, and 0.1%, and 1% aq.; iridium 1% pet.; iridium (III) chloride 0.1%, 0.32%, and 1% aq.; and iridium (IV) chloride 1% aq.¹ Previous studies have found sensitization frequencies between 0% and 9%.^{6,8,9,10,15} The aim of this investigation is to provide information about the prevalence, test preparations, and cross-reactivity of indium and iridium with other metals.

2 | METHODS

A total of 364 patients were patch tested at the allergy unit of the University Hospital of Basel from 2008 to 2017. Indications were mainly suspicion of metal allergy to orthopedic or other metal-containing devices.

To evaluate the optimal compound and concentrations, 48 metal compounds representing 27 different metals were tested (Table S1) including:

- Indium chloride 10% aq., indium sulfate 10% aq., indium 1% pet. (Chemotechnique Diagnostics, Vellinge, Sweden).
- Iridium (III) chloride 1% pet., ammonium hexachloroiridate 0.1% aq., iridium 1% pet. (Chemotechnique Diagnostics).

IQ test chambers, which are made of inert additive-free plastic/polymer (Chemotechnique Diagnostics), were applied on the upper back. The first reading was done at day (D) 2, the second between D4 and D7, according to the patients' availability. Test

reactions were rated according to International Contact Dermatitis Research Group/ESCD guidelines for patch testing.¹⁶ Informed general consent was obtained, and the local ethics committee approved the study.

3 | RESULTS

Of the 364 patients, 257 (71%) were female and 107 (29%) male, with an average age of 64 ± 10 years. Twenty-three patients (6.3%) reacted either to indium or to iridium. The patch-positive group was composed of 22 women (98%) and one man with an age between 47 and 81 years (average 62 years). Eleven patients (3%) reacted to indium salts. All of them were positive to indium chloride and one had a concomitant sensitization to indium sulfate.

Thirteen patients (3.6%) had a positive reaction to iridium salts, all to iridium chloride, and one had a concomitant reaction to ammonium hexachloroiridate. Thus, one patient was sensitized to both metals. No positive reaction was found in the tests with pure metals (Table 2). Three of 23 patients reacted only to indium or iridium, whereas 20 of 23 patients had simultaneous positive reactions to other metals: palladium (18/20), nickel (17/20), rhodium (6/20), cobalt (3/20), vanadium (2/20), gold (2/20), chromium (1/20), and niobium (1/20) (Table S2).

4 | DISCUSSION

We identified seven publications reporting systematic testing with indium and five studies on iridium including larger patient numbers. According to these limited data, contact sensitization to both metals is not as rare as expected. However, reactions to pure metals are exceptional, because both iridium and indium are not corroding at neutral conditions and therefore they are most probably less bioavailable than their chloride salts.¹⁷ Our study reflects these previous findings, as we did not find any sensitization to pure indium and iridium and detected most reactions to indium chloride and iridium chloride.

TABLE 1 Prevalence of contact sensitization to indium

n = patients	InCl ₃ 1%	InCl ₃ 3.11%	InCl ₃ 10%	InS 1%	InS 3.16%	InS 10%	In	Prevalence %	Reference
364	NT	NT	11	1	NT	1	0	3	Present study 2020
264	4	NT	NT	NT	NT	NT	NT	1.5	Nakayama 2002
205	1	1	7	2	6	10	NT	3.9	Marcusson 1998
137	NT	NT	2	NT	NT	NT	NT	1.5	Komamura 1989
63	NT	NT	2	NT	NT	NT	NT	3.2	Van Loon 1986
25	NT	NT	1	NT	NT	NT	NT	4	Ditrichova 2007
22	NA	NA	NA	NA	NA	NA	NA	0 ^a	Herrero 2000
NA	NA	5/25 ^b	NA	NA	2/7 ^b	NA	2/111 ^b	NA	Gamboni 2013

Abbreviations: In, indium; InCl₃, indium (III) chloride; InS, indium sulfate; NA, not available; NT, not tested.

^aIndium test form and concentration not described.

^bIndium chloride, indium sulfate, and indium test concentration not described.

TABLE 2 Prevalence of contact sensitization to iridium

n = patients	IrCl ₃ 0.1%	IrCl ₃ 0.32%	IrCl ₃ 1%	IrCl ₄ 1%	Alr 0.01%	Alr 0.032%	Alr 0.1%	Alr 1%	Ir	Prevalence %	Reference
700	NT	NT	0	NT	NT	NT	NT	NT	NT	0	Stingeni 2004
364	NT	NT	13	NT	NT	NT	1	NT	0	3.6	Present study 2020
264	NT	NT	NT	23	NT	NT	NT	NT	NT	8.7	Nakayama 2002
205	1	4	6	NT	0	0	0	1	NT	1	Marcusson 1998
25	NT	NT	0	NT	NT	NT	NT	NT	NT	0	Ditrichova 2007
22	NA	NA	NA	NA	0 ^a	NA	NA	NA	NA	0	Herrero 2000

Abbreviations: Alr, ammonium hexachloroiridate; Ir, iridium; IrCl₃, iridium (III) chloride; IrCl₄, iridium (IV) chloride; NA, not available; NT, not tested.

^aIridium test form and concentration not described.

In recent years it has been suggested to do the second readings from D5 to D7, and even later, particularly for metals. A limitation of our study is that our second reading was performed between D4 and D7; therefore we might have missed some later positive reactions.

If we compare our data of indium sensitization with the literature, we find a similar prevalence of contact sensitization to indium (3% vs. 0–4%), even though in previous studies different concentrations and metal salts were used for patch testing (Table 1). We found the highest number of reactions to indium chloride 10%, with a prevalence of 3%. Marcusson et al⁹ described for the same compound and concentration a prevalence of 3.4%. Of interest, however, we found a discrepancy with the same study when comparing positive reactions to indium sulfate 10%: We identified one positive only in 364 compared to 10 of 205 in the patients of Marcusson et al.⁹

There is only one publication⁵ where pure indium metal was tested, finding 2 sensitizations in 111 tested, compared to our findings of 0 of 364. A real comparison with our data is, however, not possible, because the vehicle and the concentration used in this study are not provided. For instance, if indium metal powder is tested in petrolatum, no reaction is to be expected, as the metal is unlikely to get absorbed into the skin from this hydrophobic vehicle.

We observed two cases of strong, long-lasting reactions to indium. It is notable that these two patients reacted to indium chloride, but not to indium sulfate or to indium 1% pet. They both had positive reactions to other metals such as nickel, palladium, rhodium, and gold, suggesting the possibility of cross-reactivity. However, nickel and palladium are very common sensitizers; therefore this multiple sensitization could also represent co-sensitization due to the high prevalence of the contact sensitization to these two other metals.

Looking for type IV sensitization to iridium we found five publications reporting differing levels of prevalence (Table 2). In addition, in the literature on iridium, there is a report of an occupationally exposed worker with contact urticaria and respiratory symptoms to iridium chloride,¹⁸ and three cases with an anaphylactic reaction after the infusion of colloidal indium as radiopharmaceutical drug used for liver scanning.¹⁹

The largest study with 700 patients found no contact sensitizations to iridium chloride 1%, whereas we found 13 positive reactions

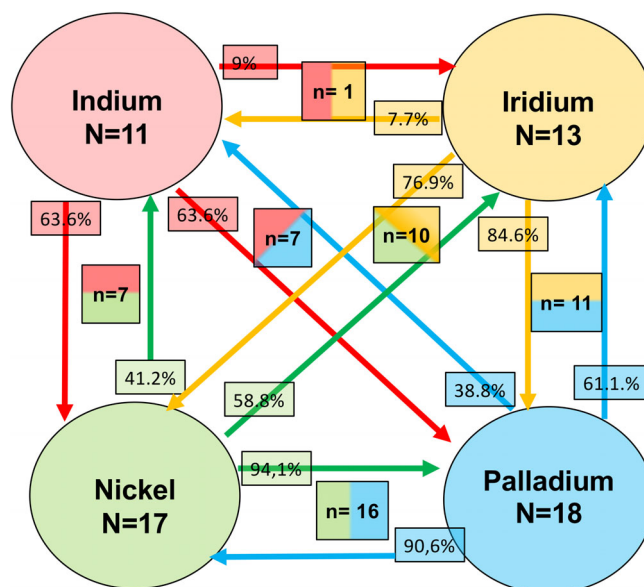


FIGURE 1 Co-sensitization or cross-sensitization between nickel, palladium, indium and iridium. N = number of positive tests to the respective metals. n = number of positive to a metal pair. % positive patch tests among a metal pair

(3.6%). The highest prevalence was observed by Nakayama et al,⁸ with 23 of 264 (8.7%). However, in this study, iridium (IV) chloride was used and this could explain the higher share of positive reactions, since iridium (IV) chloride is more reactive than iridium (III) chloride. Similar to our findings, Marcusson et al⁹ found most reactions (2.9%) with iridium chloride 1%.

Twelve patients positive to iridium were also positive to nickel and palladium, and some also to other metals such as cobalt. As with indium, the concomitant reactions to several metals raise the issue of co-exposure. Indium and iridium are indeed commonly used in alloys with gold, rhodium, palladium, and platinum, indicating co-sensitization, whereas co-sensitization to other common metals, such as chromium, is not as often observed. Therefore, apart from cross-reactivity, co-sensitization due to concomitant exposure or less likely potential contaminants in patch test substances could be an explanation of this phenomenon.

TABLE 3 Concentration of the relevant metal compounds, as well as of the metal itself on the tested area^g (calculated for 20 mg or μL respectively)

Metal	Chemical hapten	Conc. ^a %	C(chem) ^b $\mu\text{mol/l}$	c(w/A) ^c $\mu\text{g/cm}^2$	c(mol/A) ^d $\mu\text{mol/cm}^2$	c _{metal} (w/A) ^e $\mu\text{g/cm}^2$	c _{metal} (mol/A) ^f $\mu\text{mol/cm}^2$
Nickel	Nickel sulfate hexahydrate	5	217 232	1471	5.6	328	5.6
Cobalt	Cobalt chloride hexahydrate	1	47 997	294	1.2	72.9	1.2
Chromium	Potassium dichromate	0.5	19 402	147	0.50	52.0	1.0
Palladium	Palladium chloride	1	64 376	294	1.7	177	1.7
	Sodium tetrachloropalladate	3	116 406	882	3.0	319	3.0
Gold	Sodium thiosulfatoaurate	0.25	5423	74	0.14	27.5	0.14
	Potassium dicyanoaurate	0.002	79	0.6	0.002	0.40	0.002
Platinum	Ammonium hexachloroplatinate	0.1	2253	29	0.07	12.9	0.07
	Ammonium tetrachloroplatinate	0.25	7652	74	0.20	38.5	0.20
Indium	Indium	1	99 423	294	2.6	294	2.6
	Indium chloride	10	452 120	2941	13.3	1527	13.3
	Indium sulfate	10	193 121	2941	5.7	1304	11.4
Iridium	Iridium	1	59 389	294	1.5	294	1.5
	Iridium chloride trihydrate	1	32 377	294	0.83	160	0.83
	Ammonium hexachloroiridate	0.1	2268	29	0.07	12.8	0.07

^aConc. = Concentration.^bC(chem) = Hapten concentration in the used product.^cc(w/A) = weight of the hapten per area.^dc(mol/A) = mole of the hapten per area.^ec_{metal}(w/A) = weight of the metal per area.^fc_{metal}(mol/A) = mole of the metal per area.^gArea (A) = 0.68 cm².

There is no previously published data on patch tests with pure iridium. Iridium is structurally very similar to rhodium and platinum, and in its pure form it is rather inert. Thus, as expected, we did not find any reaction to this test compound. One patient only was positive for both indium and iridium. As expected cross-reactivity between indium and iridium is unlikely (Figure 1).

For a precise comparison between the different studies it would be necessary to calculate the molar dose per area of the corresponding metal tested (Table 3, violet column). The patch test area should also be indicated. We present the calculations for the relevant metal compounds in $\mu\text{g/cm}^2$ and in mol/area, and in addition the concentration of the metal itself in $\mu\text{g/cm}^2$ and mol/area (Table 3). However, these values are not available for past studies. Therefore, to promote research in this field and homogeneity among studies, it would be important to report the mol/area of each product used, so that future observations can be better compared.

Metals can be irritating and toxic for the human body. Therefore, caution is mandatory when testing with nonstandardized metal compounds. Sometimes it is difficult in metal patch tests to differentiate irritant from allergic reactions. Our readings were done by the same experienced dermato-allergists using the same criteria, thus making inter-rater differences less likely.

The interpretation of positive tests and the determination of their relevance require careful analysis and expert knowledge. For instance, a positive patch test with indium metal does not imply a

reaction to materials containing indium. Relevance of sensitization is difficult to establish for these two metals, because exposure is often not known and not easily recognizable. We checked for dental fillings, crowns, and implants in our patients. However, we did not find any dental materials or the presence of oral manifestations, and correlation with positive tests. Interaction of alloys with sweat may be different from those to the particular metals of which the alloys are composed.²⁰ Finally, further circumstances and conditions (such as contact area, geometric configuration, and time) should also be considered.

5 | CONCLUSION

If routinely tested, sensitization to indium and iridium seems to be as prevalent as to some other metals. Variability in the prevalence among the various studies could be explained by different test populations, test compounds, vehicles, and concentrations used. In our study, indium chloride and iridium chloride give more positive results than other compounds tested. Therefore, these 1% concentrations in pet. seem to be a sensitive and nonirritating preparation.

The high share of concomitant reactions to other metals should also be further evaluated in future studies. Unfortunately, the clinical relevance of indium and iridium sensitization is still often unknown, because exposure is difficult to determine. However, because use of

both metals is becoming increasingly common in jewelry, dental alloys, stents, and as tracers in nuclear medicine, clinicians should be aware of their possible allergenic potential. In patient populations at risk of exposure, these two rare metals should be included in the patch test series.

ACKNOWLEDGEMENT

The contributions of Reinhard Kissner, in particular the calculations in Table 3, are gratefully acknowledged.

CONFLICT OF INTEREST

None to declare.

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SUPPORTING INFORMATION

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

How to cite this article: Terrani I, Scherer Hofmeier K, Bircher AJ. Indium and iridium: Two rare metals with a high rate of contact sensitization. *Contact Dermatitis*. 2020;1-5. <https://doi.org/10.1111/cod.13549>

Online supplemental Table 1: Metal compounds used for patch testing.

Tested compound	Concentration (%)	Vehicle
Aluminum ³	100	pet.
Aluminum chloride ³	2	pet.
Amalgam ¹	5	pet.
Amalgam alloy ¹	20	pet.
Ammonium hexachloroiridate ¹	0.1	aq.
Ammonium hexachloroplatinate ³	0.1	aq.
Ammonium molybdate tetrahydrate ¹	1	aq.
Ammonium tetrachloroplatinate ¹	0.25	pet.
Cadmium chloride ⁵	0.5	pet.
Calcium titanate ³	10	pet.
Cobalt chloride* ¹	1	pet.
Copper oxide ³	5	pet.
Copper sulfate ¹	2	pet.
Indium ³	1	pet.
Indium chloride ³	10	aq.
Indium sulfate ³	10	aq.
Iridium ³	1	pet.
Iridium chloride trihydrate ³	1	pet.
Iron chloride ³	2	pet.
Lead acetate trihydrate ³	0.5	aq.
Magnesium chloride ⁴	5	pet.
Manganese chloride ³	2	pet.
Mercury ³	0.5	pet.
Mercury amide chloride ₁	1	pet.
Mercury chloride ³	0.1	pet.
Molybdenum ³	5	pet.
Nickel sulfate* ¹	5	pet.
Niobium chloride ⁴	1	pet.

Palladium chloride ²	1	pet.
Potassium dichromate* ¹	0.5	pet.
Potassium dicyanoaurate ¹	0.002	pet.
Rhodium chloride ⁴	3	pet.
Ruthenium oxide ⁴	2	pet.
Silver nitrate ³	1	aq.
Sodium tetrachloropalladate ³	3	pet.
Sodium thiosulfatoaurate ¹	0.25	pet.
Thiomersal ¹	0.1	pet.
Tin ³	50	pet.
Tin chloride ¹	0.5	pet.
Titanium ³	10	pet.
Titanium chloride ³	0.1	aq.
Titanium nitride ³	5	pet.
Titanium oxalate decahydrate ³	1	pet.
Tungsten ³	5	pet.
Vanadium chloride ³	1	pet.
Vanadium metal ³	5	pet.
Zinc ³	2.5	pet.
Zirconium chloride ³	1	pet.

*from European standard series.

¹ allergEAZE - SmartPractice Europe respectively Almirall Hermal (Reinbek, Germany).

² Trolab - SmartPractice Europe resp. Almirall Hermal (Reinbek, Germany).

³ Chemotechnique Diagnostics (Vellinge, Sweden).

⁴ Pharmacy University Hospital Basel

⁵ HAL Allergy Group (Leiden, Netherlands).

Online supplemental Table 2: Results of indium and iridium patch test reactions and concomitant sensitization to other metal allergens.

Patient	InCl ₃	InS	In	IrCl ₃	Alr	Ir	Pd	Ni	Rh	Co	V	Au	Cr	Nb
1	+++			+++	++									++
2				++			+++	+++						
3				++			+++	+++			++			
4	++						+++	+++	++			+++		
5	++						++	++						
6				++			+++	+++	++					
7				++			+++	++		+++				
8				++			++	+++						
9	++						++	+++		+++				
10	+++	+++					+	+		+++			+	
11	+							++						
12				++			++	++						
13				++			+++	+++	++		++			
14	++													
15				++										
16				+			+							
17				+			++	++						
18				++			++	++				++		
19	+						++		++					
20	+													
21	+						+++	++	+					
22	+++						++	+	+					
23				++			++	++						

Alr-ammonium hexachloroiridate; Au-gold; Co-cobalt; Cr-chromium; In-indium; InCl₃-indium chloride; InS-indium sulphate; Ir-iridium; IrCl₃-iridium chloride; Nb-niobium; Ni-nickel; Pd-palladium; Rh-rhodium; V-vanadium.