Contact Dermatitis

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CONTACT DERMATITIS

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Severe Allergic Contact Dermatitis From Octylisothiazolinone in Over-Ear Headphones: A Case Series

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ABSTRACT

Background: Octylisothiazolinone (OIT; CAS 26530–20-1) is used as a biocide in leather products.

Objectives: To report several cases of allergic contact dermatitis (ACD) from the use of headphones containing OIT, and to highlight the strong allergic potential of this preservative.

Patients and Methods: Four patients with ACD from headphones were patched tested using the European baseline, cosmetic, rubber, plastics/glues and acrylates series. Patients were also tested to different parts of their own headphones ('as is'). Chemical analyses of the headphones was additionally performed with Ultra Performance Liquid Chromatography—tandem mass spectrometry (UPLC-MS/MS).

Results: All patients had developed localised ACD to the contact sites of the headphones, except for one patient who developed 'angioedema-like' dermatitis. All patients were shown to have been primarily sensitised to OIT. UPLC-MS/MS analysis confirmed OIT in the leather ear pads of the headphones.

Conclusions: OIT is a relevant and strong sensitizer in leather, and may cause severe ACD. Safer use concentrations (limits) of OIT, as well as product labelling in the leather industry, may be required to ensure a better protection of consumers.

1 | Introduction

Headphones, mostly in-ear headphones, have been described as a cause of allergic contact dermatitis (ACD), due to gold [1] and acrylates [2, 3]. Recently, one case of ACD to wireless over-ear headphones caused by isothiazolinones [4] was reported.

Here, we describe four additional patients who developed severe ACD after wearing over-ear headphones, and we focus on octylisothiazolinone (OIT) as a relevant contact allergen in this regard.

2 | Patients and Methods

2.1 | Patients

Four patients were referred for patch testing because of a suspicion of ACD from over-ear headphones: Patients 1 and 2 to the department of occupational and environmental diseases at Hotel-Dieu Hospital in Paris, France, and Patients 3 and 4 to the department of dermatology at Centre Hospitalier in Lille, France.

Marion Menanteau and Goël Fenech have contributed equally as first authors.

2.1.1 | Patient 1

A 21-year-old African female, atopic but without a past history of eczema, was referred because of a prominent facial swelling with remarkable eyelid oedema, yet also scaly and itchy plaques on the outer ears. The skin lesions had initially started around her ears after wearing over-ear headphones ('JBL Tune 710BT black', Harman International Industries, 8500 Balboa Blvd, Northridge, California) for 2 weeks. Quite rapidly, within 1 week, the dermatitis progressed and eventually involved the whole face. The patient went to the Emergency Room twice, and was hospitalised the second time because she also experienced laryngeal discomfort. Upon hospitalisation, she was erroneously treated with Icatibant for suspected bradykinin-mediated angioedema. After dermatology advice, a diagnosis of contact dermatitis was put forward, and allergy tests were scheduled.

2.1.2 | Patient 2

A 25-year-old African female, with a past history of atopic dermatitis, presented with an acute, symmetric eczematous dermatitis of the outer ears, also involving the pre- and retro-auricular regions. The skin lesions had appeared after the occasional wearing of gaming headphones ('SteelSeries Arctis Nova 1 black', SteelSeries company, 656 W Randolph St, Suite 3E Chicago, Illinois) for 2 months (Figure 1).

2.1.3 | Patient 3

A 20-year-old Caucasian female, with known atopy, presented with an acute eczematous dermatitis of the outer ears as well as the pre- and retro-auricular regions. The skin lesions had

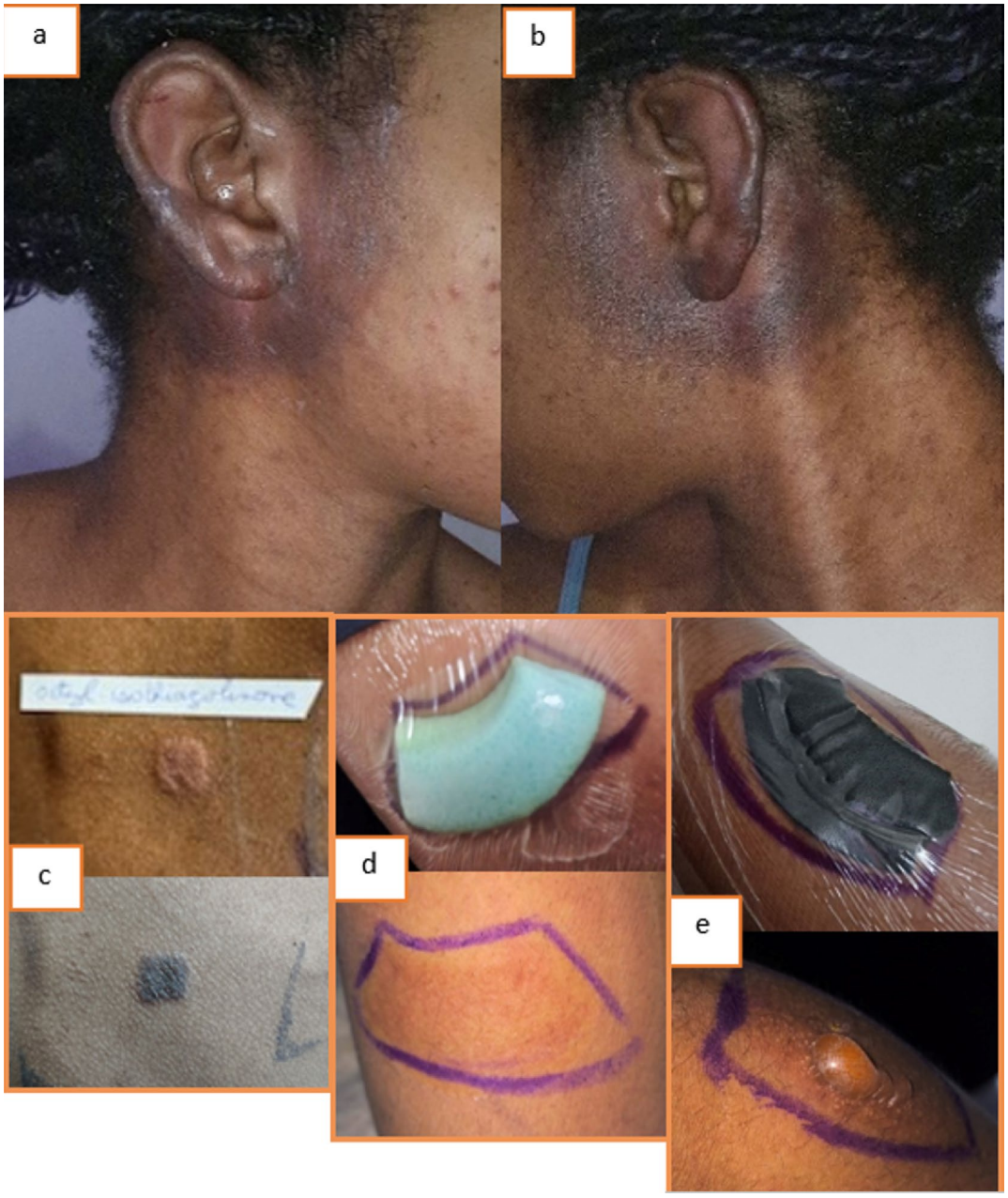

FIGURE 1 | Patient 2 with well-demarcated eczematous lesions of outer ears and pre- and retro-auricular regions (a,b), patch test positive for OIT (c), foam (d) and leather (e) headphones samples.

appeared after wearing a new set of headphones (JBL Live 660NC, Harman International Industries, 8500 Balboa Blvd, Northridge, California) (Figure 2).

2.1.4 | Patient 4

An 18-year-old Caucasian male, with known atopy, presented with eczematous dermatitis around the ears every time he played video games whilst wearing his gaming headphones (brand unknown) (Figure 3).

2.2 | Patch Testing

All patients underwent patch testing with the European Baseline Series, and also with a cosmetic, rubber, plastics/glues including diaminophenylmethane (MDA) and acrylates series, using test

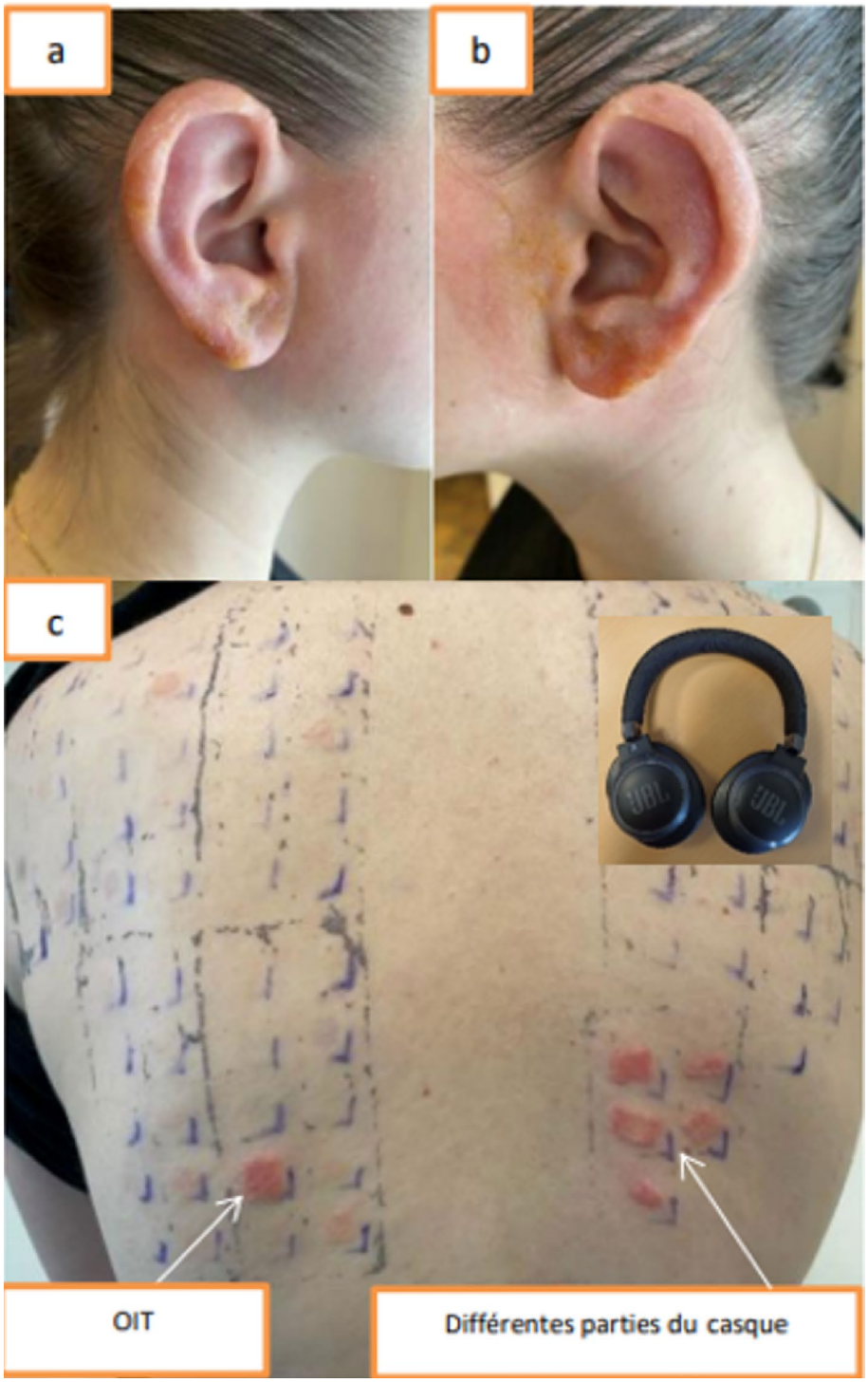

FIGURE 2 | Patient 3 with well-demarcated eczematous lesions of outer ears and pre- and retro-auricular regions (a,b), patch test positive for OIT and different parts of the headphone (c).

preparations from SmartPractice Europe (Greven, Germany), and IQ ultra-chambers from Chemotechnique Diagnostics (Vellinge, Sweden). Patients 3 and 4 had additional testing with isocyanate series. All tests were performed according to ESCD guidelines, including an occlusion time of 2 days. In Patients 1 and 2, large pieces of the headphones were applied semi-open 'as is' after being moistened with water: the leather or faux-leather part and the foam part. In Patients 3 and 4, small pieces of the headphones were applied to patch test chambers.

The patches were removed on Day (D) 2, and readings were performed on D2 and D3.

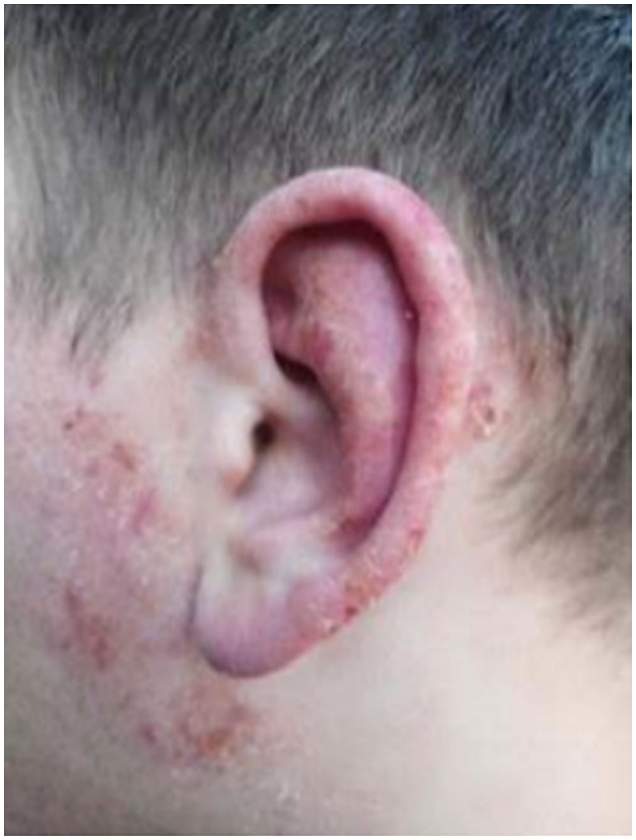

FIGURE 3 | Patient 4 with eczematous dermatitis on the left ear.

2.3 | Chemical Analyses of the Headphones

In Patients 1 and 2, chemical analyses of their wireless over-ear headphones could be additionally performed using UPLC-MS/MS method. The headphones were disassembled, and all the parts were identified prior to the analytical process as shown in Figure 4. Five parts were labelled as follows:

1. transparent plastic piece to which the earphone cover is glued on one side and the black support ring on the other side;
2. headphone polyurethane foam;
3. thin layer of black foam located behind the black support ring;
4. protection layer of the foam which is directly in contact with the ears;
5. protective fabric strip at the bottom of the headphone.

Approximatively 0.5 g of each part was cut into small pieces and placed with 5 mL of methanol (Lichrosolv, Merck) into 10 mL glass vessels closed with a Teflon-coated screw cap. Samples were extracted in an ultrasonic bath for 15 min.

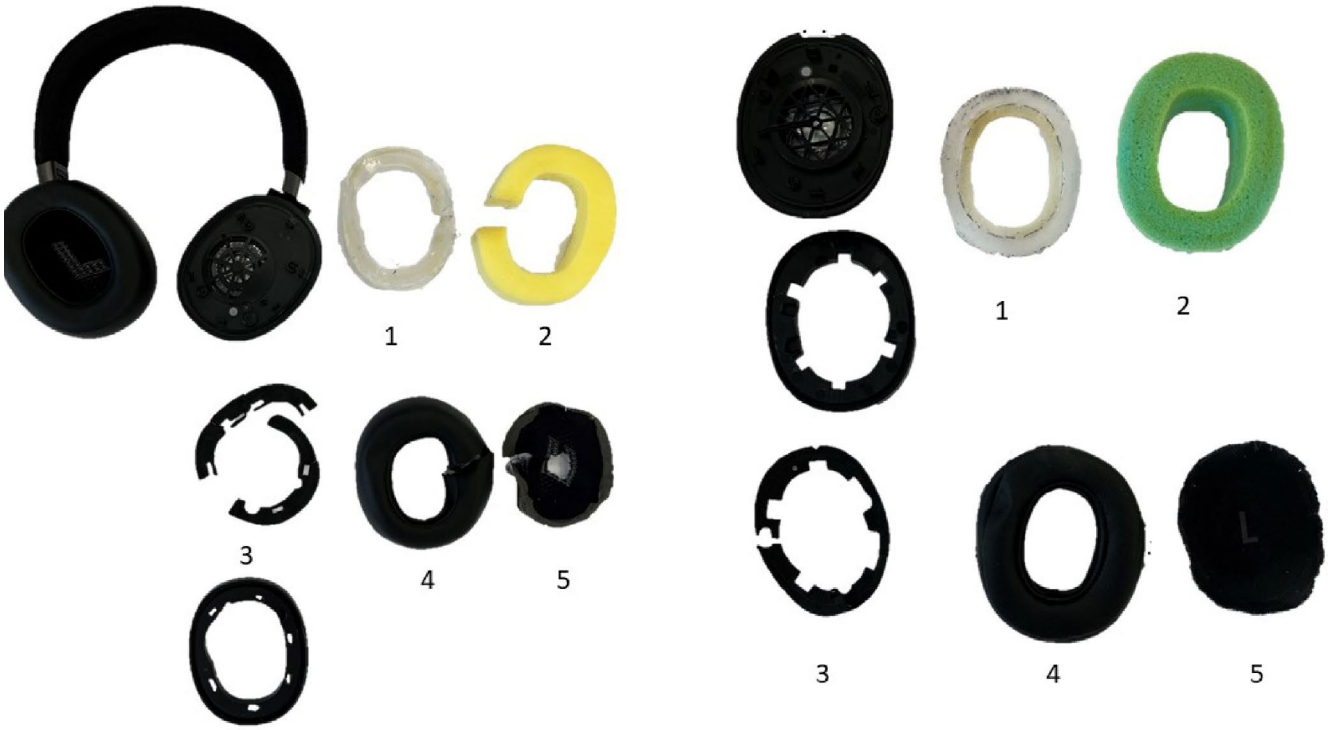

FIGURE 4 | Different parts of the culprit headphones of the Patient 1 (left side) and 2 (right side), that were analysed using UPLC-MS/MS.

A Waters Acquity UPLC H Class system with a Xevo TQD MS/MS was used for the analysis. The chromatographic separation was performed on a Inersustain PhenylHexyl (3 μm, 2.1 × 100 mm) UPLC PEEK Column (GL Science, Cat: 5020–87 437).

The mobile phase consisted of Milli Q water as solvent A, acetonitrile (VWR, Rosny sous bois, France) as solvent B and acetic acid 5% (v/v) (Roth, Karlsruhe, Germany) as solvent C. A gradient method was performed. A constant flow rate of 0.4 mL/min and an injection volume of 2 μL were used.

OIT was detected by MS/MS. Quantification transition was 214 > 102 and confirmation transitions were 214 > 57 and 214 > 71 and quantified by the use of reference solutions of OIT in methanol. Reference OIT (2-Octyl-4-isothiazolin-3-one, CAS: 26530–20-1) was obtained from Sigma-Aldrich (Saint-Louis, USA).

3 | Results

3.1 | Patch Test Results

Strongly positive patch test results (+++) to OIT 0.1% pet. were observed on D3 in all four patients (Figures 1, 2 and 5). All patients also reacted to both the leather and the foam parts of the headphones, with +++ bullous reactions occurring in two patients. (Figures 1 and 5). None of them reacted to MDA.

Patient 1 was also sensitised to chromium+, cobalt+, methyldibromo glutaronitrile+, dithiodimorpholine++ with no relevance found (the leather part of the headphones was faux leather).

Patient 2 also had positive results to methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) 0.02% aq and methylisothiazolinone (MI) 0.2% aq++ as well as to 2-bromo 2-nitropropane-1.3-diol++, tea tree oil++, methyldibromo glutaronitrile+, *N*-(cyclohexylthio)phtalimide++ and dithiodimorpholine++. MCI/MI were not analysed in the patient's headphones so we cannot exclude their presence. Their positivity in patch test could be relevant. Furthermore, we found past relevance for the positive results to MCI/MI, as well as with the 2 bromo 2 nitropropane with past history of hand eczema and the use of soaps and dishwashing liquids containing these allergens. We also found past relevance to the tea tree positive results with forehead and scalp eczema after the patient used tea tree oil on her hair.

Patient 3 had additional positive results for fragrance mix I and II++, and *Myroxylon pereirae* resin++. Patch tests with isocyanates were negative.

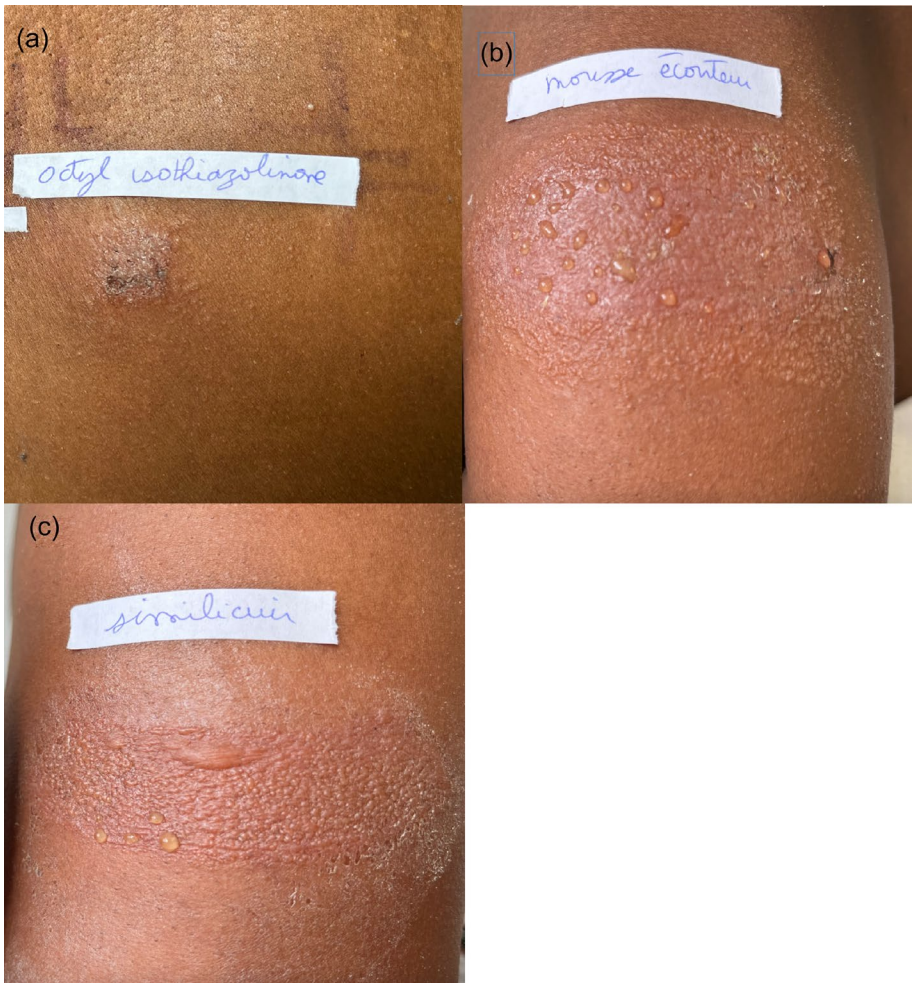

FIGURE 5 | Patient 1 with patch tests positive for OIT (a), foam (b) and leather (c) headphones samples.

TABLE 1 | Results of the analyses of the different parts of the two headphones, compared with the literature results.

	OIT concentration (μg/g)				
	Headphone parts				
Headphone	**1**	**2**	**3**	**4**	**5**
Patient 1	120	590	230	860	45
Patient 2	310	780	840	1100	120
Carropo et al. [4]	> 20	> 50	Not analysed	> 150	> 100

We can argue the fragrance sensitization could be relevant with a presence in shampoos, and the occlusion effect of the headphones. Nevertheless, there was no sign of eczema on the scalp.

Patient 4 also had positive results for nickel sulphate++, benzalkonium chloride+ and 2-hydroxyethyl methacrylate+, with a possible past relevance. Patch tests with isocyanates remained negative.

All patients recovered from their dermatitis after avoiding their headphones.

3.2 | Results From Chemical Analyses of the Headphones

In all four cases the labelling of the headphones contained no information on their composition. The results of the chemical analyses for the two headphones are presented in Table 1. The highest concentrations of OIT were found in the foam and in its protective layer, that is, Parts 2 and 4, respectively.

Based on the clinical data, patch test results, and chemical analyses a final conclusive diagnosis of contact allergy to, and ACD from, OIT contained in the headphones could be made.

4 | Discussion

We present four cases of severe ACD from OIT in over-ear headphones. The presence of this biocide was confirmed, in important quantities, in several parts of two of the culprit headphones using UPLC-MS/MS.

OIT is an isothiazolinone derivative increasingly used in non-cosmetic [5]. It is used as a biocide in paints, glues, cutting and cooling fluids, wood preservatives, household detergents, textiles [6] and also in the leather industry [7]. In the leather production process, isothiazolinones in general are used for their fungicidal properties.

In the present case series, all subjects had strongly positive reactions to OIT and to the pieces of leather or faux-leather and foam items tested 'as is'. The chemical analysis equally showed that the highest concentrations of OIT were mainly found in the leather and the foam parts of the headphones. Concentrations in the other parts were lower, possibly suggesting minor diffusion of OIT from the leather/foam parts towards the terminal fabric strips of the headphones. These findings are consistent with the results of Carropo et al. [4] reporting on the same kind of headphones. Interestingly enough, the foam and the faux-leather of the headphone are probably made from polyurethane, however patch tests with isocyanates remained negative for Patients 3 and 4.

Compared with other isothiazolinone derivatives, OIT appears to be less frequently used, and also a less prevalent sensitizer [6, 8]. It was initially presented as a contact allergen of moderate potency [9], but is now considered by the European Chemicals Agency (ECHA; harmonised classification and labelling-CLH report) as a strong to even extreme sensitizer [10]. OIT is currently classified as Skin Sensitizer Category 1A with a specific limit concentration of 0.0015% [5]. However, our chemical analyses of the headphones showed excessive concentrations of OIT up to 1100 μg/g, that is, 0.11% without label statement or pictogram as recommended when a skin sensitizer is above the concentration limit [5].

Contrary to MI and MCI/MI, ACD caused by OIT has never been described with clinical manifestations other than skin involvement, or with unusual clinical presentations [11, 12]. In our series, Patient 1 was hospitalised because she complained of laryngeal discomfort and developed 'angioedema-like' dermatitis with severe facial swelling. She was misdiagnosed as bradykinin-mediated angioedema. Subsequently, a correct diagnosis of ACD was made because of the presence of pruritic, erythematous scaly plaques that had started on the outer ears following the use of new over-ear headphones, reminding us that the initial site of dermatitis often provides an important clue for the diagnosis. This particular clinical picture is very reminiscent of ACD from paraphenylene diamine (PPD), which can also present with severe facial swelling. Immediate allergy to OIT was not considered because the reaction did not diminish but worsened the first 72 h after removal of the headphones. No cases of type 1 hypersensitivity to isothiazolinones have been described in literature.

Except for Patient 1, the ACD of our patients was limited to the skin contact sites of the headphones with a strikingly geometric pattern mirroring the surface of the headphones. A very similar case of ear dermatitis, without facial involvement, caused by isothiazolinones in headphones, has been recently described [4]. One case of 'angioedema-like' airborne dermatitis from MI in paints has been reported [13]. As far as we know, ours is the first case of an angioedema-like ACD caused by a non-cosmetic product containing OIT.

Only Patient 2 showed concomitant sensitization to MI and MCI/MI and, based on the gradation of the patch test reactions (OIT > MI, MCI/MI), OIT can most likely be considered as the primary sensitizer. It suggests that patients primarily sensitised to OIT might not easily cross-react with MI, in contrast to the reverse [14], a topic that remains controversial in the literature [15–17]. Of note, isothiazolinone derivatives were patch-tested in high enough concentrations allowing us to compare them ([OIT] 0.1% pet, [MCI/MI] 0.02% aq, [MI] 0.2% aq). Unfortunately, MI and MCI could not be chemically analysed, so we cannot draw conclusions regarding cross-or co-sensitization in our case.

In 2022, OIT was still included in the European Baseline Series (EBS) as a recommended addition [18], and the current case series reinforces its value there, all the more since it appears to be a quite strong sensitizer, present in high levels, in leather goods commonly used by consumers.

5 | Conclusion

In the current case series we showed that OIT was present in leather over-ear headphones, in high concentrations, leading to primary skin sensitization and severe ACD, sometimes with atypical clinical features. Our observations suggest that forthcoming legislation might need to enforce safer and stricter use concentrations of OIT, and mandatory labelling of non-cosmetic products, in order to ensure a better protection of consumers.

Author Contributions

Marion Menanteau: writing – original draft, conceptualization. **Goël Fenech:** conceptualization, writing – original draft, writing – review and editing. **Benjamin Adam:** conceptualization, writing – original draft. **Eddy Langlois:** writing – original draft, methodology, investigation. **Pierre Marcant:** writing – review and editing. **Eric Pelletier:** investigation, methodology. **Delphine Staumont-Sallé:** writing – review and editing. **Lynda Bensefa-Colas:** writing – review and editing, supervision. **Marie-Noëlle Crepy:** conceptualization, writing – original draft, writing – review and editing, supervision.

Consent

All patients gave their written informed consent for their history to be reported. All patients except one (Patient 1) also gave consent for their photographs to be published.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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