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ORIGINAL ARTICLE

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Using chemical speciation modelling to discuss variations in patch test reactions to different aluminium and chromium salts

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Abstract

Background: Allergic contact dermatitis to metals is diagnosed by applying a metal salt in a patch test. The bioavailability of the metal salt might depend on the choice of metal salt, the concentration, sweat composition, and pH.

Objectives: The main purpose of this study was to apply chemical speciation modelling, which is based on experimentally derived input data and calculates the concentrations of chemical forms (species) in solutions, to reproduce and discuss clinical patch test results of aluminium and chromium.

Methods: Joint Expert Speciation System (JESS), Hydra/Medusa, and Visual MINTEQ were employed to study the bioavailable fraction and chemical form of clinically applied aluminium and chromium salts as a function of salt type, applied concentration, sweat composition, and pH.

Results: Investigated aluminium and chromium salts can have a very low bioavailability with a large dependency on sweat composition, pH, metal salt, and concentration. Both aluminium and chromium ions could shift the pH towards acidic or basic values based on their chemical form.

Conclusions: Reported seasonal and interpatient variability in positive reactions to aluminium is likely related to sweat pH and composition. Potassium dichromate increases the pH, whereas aluminium and trivalent chromium chloride strongly decrease the pH, possibly increasing skin diffusion.

KEYWORDS
aluminium, chromium, contact dermatitis, patch testing

1 | INTRODUCTION

Metal contact allergies have been widely reported and arise from skin contact and exposure to metal-containing materials and environments.[1] Aluminium has been extensively used in many applications including cosmetic products,[2] food industry,[2,3] and vaccination programs.[4,5] In rare cases, skin exposure to aluminium might result in the development of contact allergy.[6] Patch testing with various aluminium salts in addition to an empty aluminium Finn chamber has been employed to investigate aluminium allergy.[7,8] Siemund et al[9] studied different aluminium salts in an attempt to find an optimum concentration and compound as a reference material, which would be capable of eliciting a positive skin reaction in persons with aluminium allergy. However, positive reactions were shown to be not consistent over time.[10]

Chromium is among the most prevalent metal allergens.[11] Contact allergy to chromium can develop as a result of exposure to construction sites (eg, cement-releasing hexavalent chromium

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[Cr^{VI}]),[12] chromium-tanned leather articles,[13] articles coated with Cr^{VI}, some metal items, and other items including detergents.[14,15] Trivalent Cr (Cr^{III}) is the hapten binding to a carrier (a protein) that together form the antigen involved in chromium allergy.[16-18] However, Cr^{VI} is a much more potent sensitizer due to its rapid skin and cell permeability, after which it may be reduced to its trivalent form (the hapten).[15,19]

The valence or oxidation state of metals is denoted as upper Roman numbers; for example, Al^{III} denotes trivalent aluminium. This should not be mistaken with the charge, which is denoted as upper Arabic numbers followed by the charge sign (eg, Al^{3+}). Aqueous Al^{3+} is denoting a positively charged ion (cation) dissolved in water. Al^{III} or Cr^{III} can be present in many chemical forms, including solids and aqueous cations and negatively charged ions (anions). The chemical form, not the oxidation state alone, determines their ability to penetrate the skin and bioavailability, which is important to elicit an allergic reaction during patch testing. The determination and description of chemical forms (species) are called chemical speciation. Chemical speciation can be determined experimentally or theoretically. Chemical equilibrium speciation modelling uses experimentally derived input values of reactions in equilibrium and calculates the concentration of each species of interest, for example, the various solid forms, anions, and cations of aluminium in a certain artificial sweat composition. In the following, the bioavailable fraction of the metal is defined as the aqueous fraction of the metal. Solid species, which are not able to penetrate the skin or to bind to proteins, are in the following considered nonbioavailable, although there might be important exceptions when transported through the skin as solid nanoparticles.[20]

In this study, we aimed at using chemical speciation modelling to investigate the change of bioavailable fraction and chemical speciation of previously clinically tested aluminium and chromium salts as a function of sweat composition, sweat pH, metal salt type, and concentration. This was accomplished by using three validated chemical speciation programs: Joint Expert Speciation System (JESS),[21,22] Hydra/Medusa,[23] and Visual MINTEQ.[24] Results were compared with corresponding clinical patch test results.[9,17]

TABLE 1 The three different synthetic sweat compositions used for the chemical equilibrium speciation modelling

Sweat A[25]	Sodium chloride (NaCl, 5 g/L) Lactic acid ($C_3H_6O_3$, 1 g/L) Urea (CH_4N_2O, 1 g/L)
Sweat B[26]	Sodium chloride (NaCl, 20 g/L) Lactic acid ($C_3H_6O_3$, 15 g/L) Urea (CH_4N_2O, 5 g/L) Acetic acid (CH_3COOH, 2.5 g/L) Ammonium chloride (NH_4Cl, 17.5 g/L)
Sweat C[27]	Sodium chloride (NaCl, 5 g/L) Lactic acid ($C_3H_6O_3$, 1 g/L) Urea (CH_4N_2O, 1 g/L) Threonine ($C_4H_9NO_3$, 1 g/L) Methionine ($C_5H_{11}NO_2S$, 1 g/L) Serine ($C_3H_7NO_3$, 1 g/L) Alanine ($C_3H_7NO_2$, 1 g/L) Glycine ($C_2H_5NO_2$, 1 g/L)

2 | METHODS

Table 1 shows the compositions of three artificial sweat solutions, which were used as input for the JESS (version 8.8b) modelling. Other standard input data, conditions, methods, assumptions, and included/excluded reactions are listed in Appendix S1. The pH was scanned from 4 to 9 to assess the influence of pH on the bioavailable fraction.

Aluminium chloride hexahydrate ($AlCl_3{\cdot}6H_2O$, molecular mass 241.43 g/mol, in the following denoted as $AlCl_3$) and aluminium lactate ($Al[C_3H_5O_3]_3$, molecular mass 294.19 g/mol, in the following denoted as Al-Lac) were used as patch test substance input values at varying concentrations in the JESS modelling. These aluminium salts showed the highest positive skin reactions among different aluminium salt candidates previously.[9] Chromium chloride ($CrCl_3{\cdot}6H_2O$, molecular mass 266.45 g/mol, in the following denoted as $CrCl_3$) was used as an input patch test substance for chromium.[17] It was, during pilot modelling, found that the counterions (K^+ and Cl^-) of $CrCl_3$ and $K_2Cr_2O_7$ did not change the modelled speciation for chromium. Because the equilibrium speciation of chromium in the investigated conditions at a given pH is theoretically independent of the input chromium ion form (eg, Cr^{3+} or $Cr_2O_4^{2-}$), only Cr^{3+} was used as input chromium ion value.

Hydra/Medusa (Hydra version: 18 August 2009 and Medusa version: 16 December 2010) modelling was utilized to evaluate the change of pH of water in the presence of aluminium and chromium ions (see Appendix S1 for details).

Visual MINTEQ (version 3.1) was used to calculate the natural pH (no pH adjustment) of each sweat solution before and after adding the chromium (CrO_4^{2-}) and aluminium ($AlCl_3$) salts. This could only be done for these salts and in sweat A and B, due to database limitations.

3 | RESULTS

Figure 1A depicts the variation of the total amount of aqueous and solid aluminium species at different pH values for $AlCl_3$ in sweat A. For a higher concentration of $AlCl_3$, a higher amount of bioavailable Al is expected, based on JESS. However, the bioavailable fraction of the total applied aluminium was very low, ranging from 0.000001% to 0.03% of the applied dose for 0.2% $AlCl_3{\cdot}6H_2O$ to only 1.7×10^{-8} to 0.001% for 20% $AlCl_3{\cdot}6H_2O$ over the different pH values in sweat A. Figure 1B shows the variation of the bioavailable concentration of aluminium in the three synthetic sweat compositions. The bioavailable concentration was one and two orders of magnitude greater in sweat C and sweat B, as compared with sweat A, respectively. This

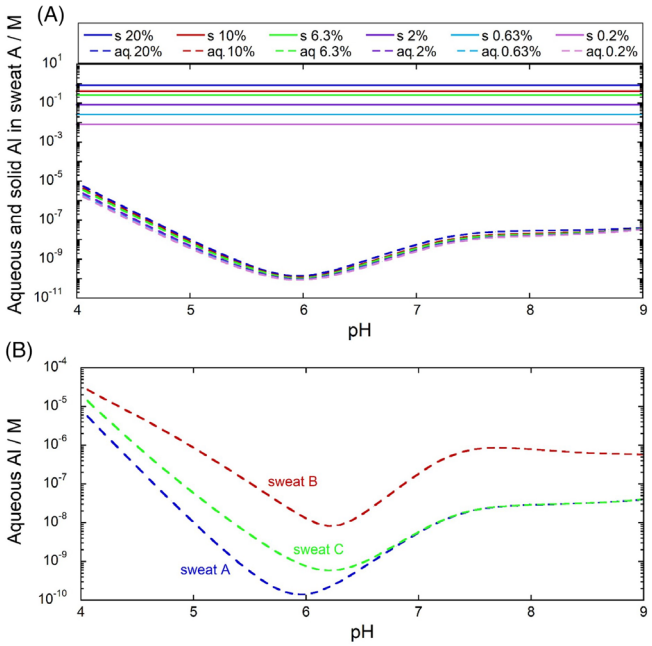

FIGURE 1 JESS-modelled (**A**) bioavailable, aqueous (aq., stacked lines), and nonbioavailable, solid (s, solid lines) amounts for different applied amounts (in wt%) of $AlCl_3{\cdot}6H_2O$ salt as a function of pH in sweat A, and (**B**) bioavailable, aqueous, and molar concentrations for the highest dose (20 wt%) $AlCl_3{\cdot}6H_2O$ salt as a function of pH in three different sweat compositions

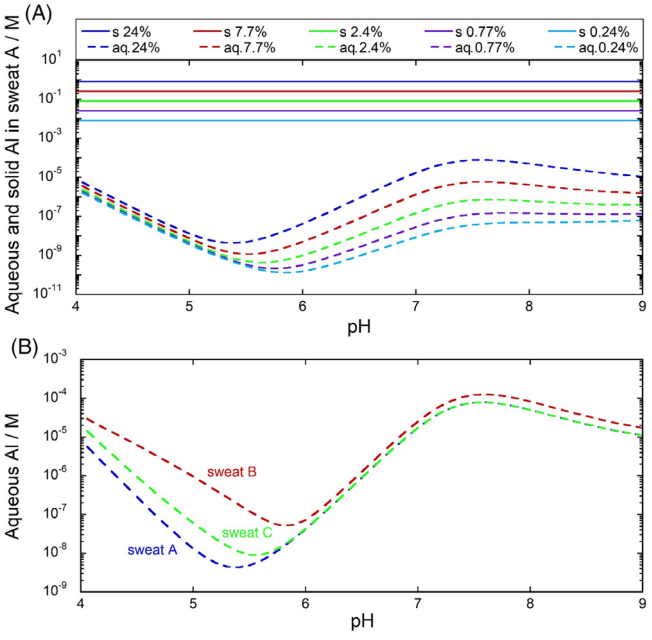

FIGURE 2 JESS-modelled (**A**) bioavailable, aqueous (aq., stacked lines), and nonbioavailable, solid (s, solid lines) amounts for different applied amounts (in wt%) of $Al(C_3H_5O_3)_3$ (Al-Lac) salt as a function of pH in sweat A, and (**B**) bioavailable, aqueous, and molar concentrations for 24 wt% $Al(C_3H_5O_3)_3$ (Al-Lac) salt as a function of pH in three different sweat compositions

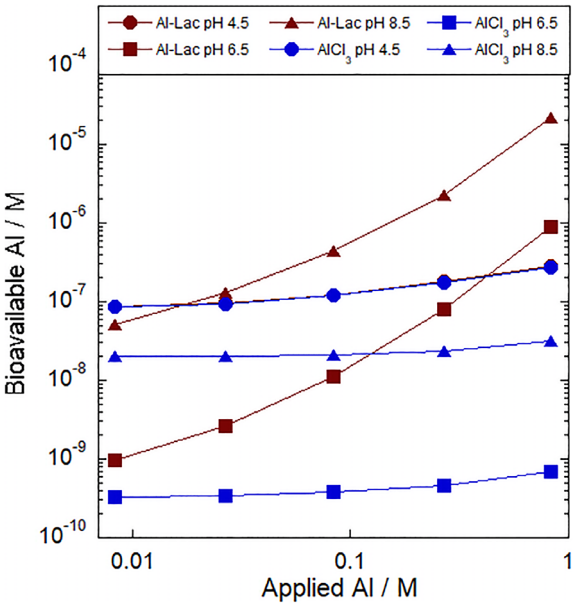

FIGURE 3 JESS-modelled aqueous (bioavailable) concentration of aluminium (Al) in sweat A as a function of the applied aluminium concentration for both $AlCl_3{\cdot}6H_2O$ (short: $AlCl_3$) and $Al(C_3H_5O_3)_3$ (short: Al-Lac) shown for three different pH values

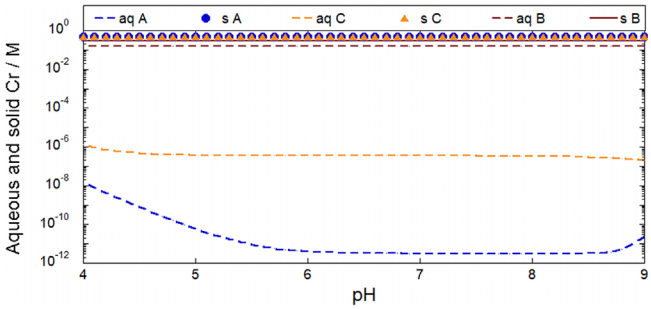

FIGURE 4 JESS-modelled bioavailable, aqueous (aq.), and nonbioavailable solid (s) amounts for the highest concentration of $CrCl_3{\cdot}6H_2O$ (13 wt%) salt as a function of pH and sweat composition. Note that the final speciation of chromium includes both Cr^{III} and Cr^{VI}

illustrates that even tiny variations in sweat compositions can have a remarkable impact on the bioavailability of aluminium. Corresponding bioavailable fractions of the total applied aluminium concentration were still very low, 9.9×10^{-7}% to 0.004% and 7.1×10^{-8}% to 0.002% of the applied concentration over the pH range for sweat B and sweat C (both 20% $AlCl_3{\cdot}6H_2O$), respectively. Corresponding predominant species of Figure 1 are depicted in Figure S1. Al-Lac species were dominating at high pH values (>6) for all sweat solutions, while the speciation of aluminium ions at lower pH (<6) depended strongly on available organic ligands (acetate, glycine) in sweat B and C as compared with sweat A. These ligands form stable complexes with the metal ions.

Another aluminium salt utilized by Siemund et al[9] is Al-Lac. Figure 2A shows solid and aqueous concentrations of aluminium for

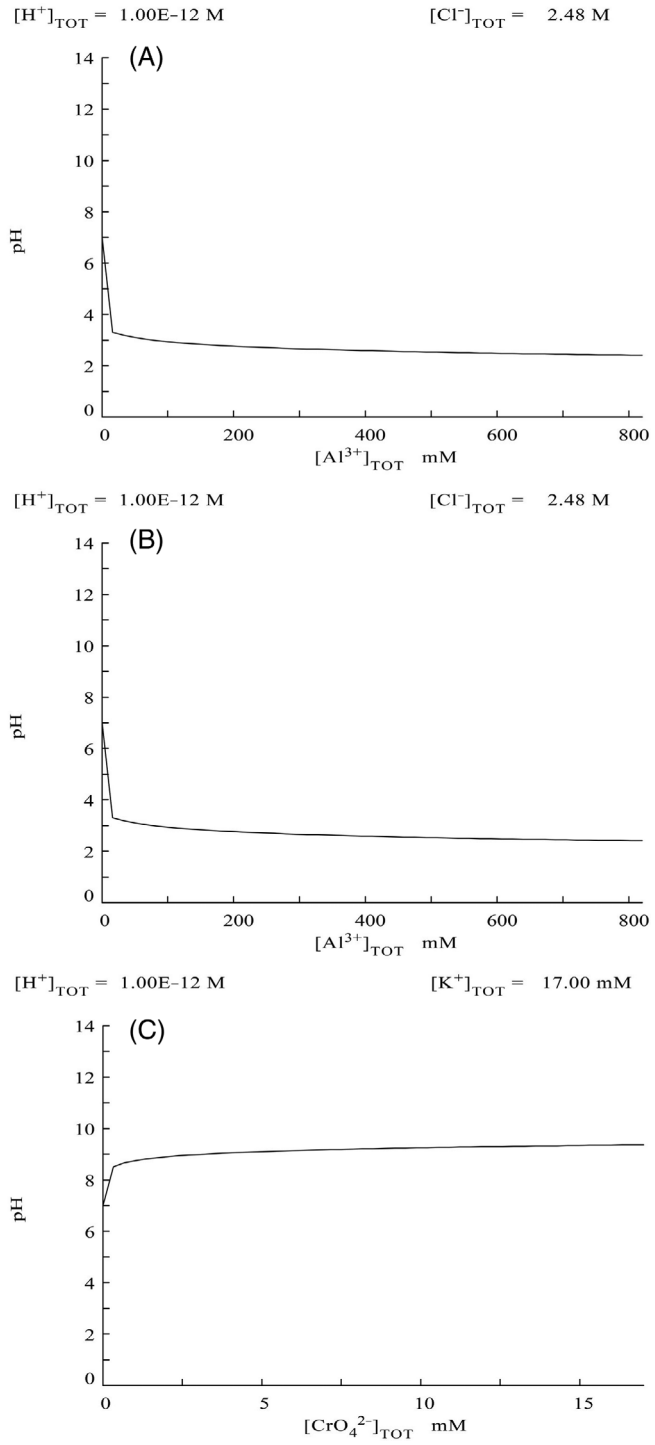

FIGURE 5 Hydra/Medusa modelling of the variation of pH in water as a function of metal ion concentration for (**A**) the highest concentration of $AlCl_3{\cdot}6H_2O$ (20 wt%), (**B**) the highest concentration of $CrCl_3{\cdot}6H_2O$ (13 wt%), and (**C**) the highest concentration of $K_2Cr_2O_7$ (0.5 wt%)

Al-Lac in sweat A. Increasing the concentration of Al-Lac resulted in a higher concentration of bioavailable species, especially at pH values above 6. The influence of sweat composition on the concentration of bioavailable species of aluminium for the highest concentration of Al-Lac (24 wt% petrolatum [pet.]) is illustrated in Figure 2B. Sweat B stabilized aqueous species to a greater extent than sweat C and A, especially at pH values below 6. Similar to $AlCl_3$, the bioavailable fraction of aluminium of Al-Lac greatly depended on the sweat composition and pH.

The high abundance of the ligand lactate for the Al-Lac patch test substance resulted in aqueous species dominated by lactate complexes with aluminium for all three sweat solutions (Figure S2). This is due to lactate being deprotonated and hence being available for complexation to aluminium ions at those pH values. At lower pH, by contrast, the dominating species depended strongly on the sweat composition.

A comparison of the aqueous (bioavailable) aluminium concentrations of $AlCl_3$ and Al-Lac patch test substances at different pH values in sweat A is shown in Figure 3. The bioavailable aluminium concentration clearly increased for Al-Lac with increasing applied total concentrations at higher pH values, in contrast to $AlCl_3$. At pH 4.5, there was no difference.

Bioavailable and solid fractions of chromium are displayed in Figure 4. Chromium in sweat B had the highest amount of aqueous species (almost entirely bioavailable throughout the pH range), in contrast to sweat A and C. The large difference in bioavailability of chromium in the different sweat solutions was related to complexation to ammonium species in sweat B and to alanine in sweat C (throughout the pH range in both cases; Figure S3). There was no predicted complexation to any ligand in sweat A, in which different free or hydroxylized Cr^{III} ions were dominant at low and neutral pH and CrO_4^{2-} (Cr^{VI}) at a pH value of 8.9 and above, at significantly lower concentrations as compared with the complexed chromium species in sweat B and C (Figure 4).

Shifts in pH values in the presence of $AlCl_3$, $CrCl_3$, and $K_2Cr_2O_7$ are exhibited in Figure 5. For the trivalent metal chloride salt solutions ($AlCl_3$ and $CrCl_3$), the pH strongly decreased to values close to pH 2, while it increased to a pH of around 9 for $K_2Cr_2O_7$. The natural pH values (without any pH adjustments) were between 6.3 and 6.6 for sweat A and B (Table 2). This pH increased to a value between 7.1 and 7.59 in the presence of $K_2Cr_2O_7$ and decreased to a value between 3.3 and 3.85 in the presence of $AlCl_3$, which agrees with the findings in water.

4 | DISCUSSION

Our chemical speciation modelling showed a particularly low bioavailable fraction of aluminium for all sweat compositions, pH values, and

TABLE 2 Calculated pH values for sweat A and B (no pH adjustments) with and without 0.017 M CrO_4^{2-} (corresponding to 0.5 wt% $K_2Cr_2O_7$) and 0.82 M Al^{3+} (corresponding to 20 wt% $AlCl_3{\cdot}6H_2O$). Calculated by Visual MINTEQ

Sweat	Sweat A	Sweat B	Sweat A + CrO_4^{2-}	Sweat B + CrO_4^{2-}	Sweat A + Al^{3+}	Sweat B + Al^{3+}
pH	6.31	6.60	7.59	7.10	3.30	3.85

aluminium salts, with bioavailable fractions far below 0.1% of the added salt. This could explain the low rate of positive reactions and the high required skin dose for positive reactions in patients with aluminium allergy.[9] This might also explain why conventional $AlCl_3 \cdot 6H_2O$ 2 wt% pet. fails to elicit a positive skin reaction in individuals with aluminium allergy,[28] as more than 99.9% of it would not become bioavailable. Besides, according to our data, the bioavailable aluminium would not linearly increase with the applied $AlCl_3$ dose, which means that a further increase in dose would not necessarily make this salt suitable for diagnostic purposes of aluminium allergy. We also found several orders of magnitude differences in aluminium bioavailability for different pH values, sweat compositions, and aluminium salts. This might explain observed interperson and interseasonal differences in aluminium patch testing for both aluminium salts.[10] Aluminium fails to form stable aqueous complexes at neutral or weakly acidic pH. This is of special importance for the $AlCl_3$ salt. There have been significantly more positive patch test reactions to Al-Lac 2.4 wt% (0.081 M) compared with $AlCl_3$ 2.0 wt% (0.082 M),[9] which could be explained by the higher bioavailability of Al-Lac based on our study. $AlCl_3$ salt can, however, also decrease the skin pH, especially for the high concentrations applied in current patch testing. This might explain why the difference in patch test reactions between Al-Lac and $AlCl_3$ salt was not reproduced for higher concentrations in that study.[9] It remains to be studied whether the pH decrease of $AlCl_3$ contributes to a greater skin uptake (due to skin damage) at high applied doses. Our data would suggest a greater bioavailability of Al-Lac as compared with $AlCl_3$ at pH values higher than 6.

In contrast to aluminium, our speciation modelling showed a high bioavailability of chromium species in one of the sweat solutions. In addition, there was an increase of pH by the most commonly used chromium patch test substance $K_2Cr_2O_7$. Increased skin pH and the negative charge of applied Cr^{VI} result in high penetration through the skin.[29] However, Cr^{III} was not stable at pH values above 4 without the complexation with organic ligands. Similar to $AlCl_3$, the application of $CrCl_3$ can result in a strong decrease of pH, which might be irritative to the skin or counteract the complexation to ligands that would keep Cr^{III} in an aqueous state. Ligand complexation and induced pH differences might explain the large difference among different Cr^{III} salts found in skin diffusion and patch test studies, in which, for example, trivalent chromium oxalate salts elicited positive patch test reactions in a significantly higher number of patients with chromium allergy as compared with $CrCl_3$ at similar molar concentration.[15,30]

4.1 | Limitations

This study showed that chemical speciation modelling could be used as a tool in the choice of metal salt patch test substances and interpretation of related patch test results. There are, however, important limitations. First, this modelling is based on chemical speciation equilibria and does not provide any information on kinetic data (how rapidly the final predominant species is formed). Kinetics might be very important, especially in the case of chromium speciation, where even a short-living chromate species (Cr^{VI}) might rapidly penetrate the skin and cell membranes. Further, this modelling does not include proteins, which are the likely ligands for metal ions exposed to skin, and the final carrier in the metal antigen. Our equilibrium chemical speciation databases did not contain much reliable information on protein-metal binding, but this could be added in future. Further, the choice of sweat compositions was based on published artificial sweat compositions and might be able to improve for future modelling efforts. The best choice of artificial sweat compositions has been highly debated.[31,32] It is clear that real sweat varies considerably in both pH and composition, and contains, for example, salts, organic acids, carbohydrates, amino acids, and nitrogenous substances. Last, the database itself could contain errors or, more likely, did not include still relevant reactions for the investigated systems. It should, however, be noted that JESS was developed for biological fluids[33] and that all reactions were based on experimental data and published studies (references of predicted species by JESS are listed in Appendix S1).

This study only investigated bioavailable species in sweat but did not consider the effect of the vehicle, amount of sweat, chamber geometry, the variability of skin penetration and reactivity, or any other parameter that also might influence the bioavailability of the metals and their elicited allergic skin reactions.

5 | CONCLUSIONS

The predicted bioavailability of aluminium from the patch test substances $AlCl_3$ and Al-Lac was very low (far below 0.1% in all cases). It was further considerably dependent on the artificial sweat composition, its pH, and the aluminium salt chosen as a patch test substance. Previously reported seasonal and interpatient variability in positive reactions to aluminium is hence likely related to sweat pH and composition. The predicted bioavailability of chromium was considerably dependent on the artificial sweat composition due to the formation of complexes. Both $AlCl_3$ and $CrCl_3$ strongly decreased the pH of water and artificial sweat, while $K_2Cr_2O_7$ increased the pH. This decrease and increase in pH might enhance skin irritation and diffusion.

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AUTHOR CONTRIBUTIONS

Saman Nikpour: Software; writing-original draft; writing-review & editing. **Yolanda Hedberg:** Software; supervision; writing-original draft; writing-review & editing.

CONFLICTS OF INTEREST

The authors declare they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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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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