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PERCUTANEOUS PENETRATION OF METALS AND THEIR EFFECTS ON SKIN

ASSORBIMENTO PER VIA PERCUTANEA DI ALCUNI METALLI E LORO EFFETTI SULLA PELLE

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Parole chiave: metalli, dermatiti da contatto, assorbimento per via percutanea

Abstract

Background: The presence of metals and their derivatives in the workplace and their accumulation in the general environment causes concern as a potential health hazard.

Objectives: To consider the potential exposure of large part of the population to metal-releasing products.

Methods: Despite the size of the problem there is a lack of reliable experimental data. Information on allergic and toxicological effects of these substances are widely disseminated in literature. However there is a lack of percutaneous penetration data relevant for dermal risk assessment. Several researchers found major technical difficulties that discouraged the carrying out of the studies. Moreover, results are obtained under very different experimental conditions, so comparison of results is difficult. A large part of the reported data on in vivo/in vitro percutaneous penetration of various metals such as Nickel, Chrome and Cobalt was published in the '60s and '70s and the results were not obtained using up-to dated methods.

Results: Metals can cause different adverse effects on skin such as irritant and allergic contact dermatitis, urticaria, granuloma and systemic toxic effects.

Conclusions: Bioavailability of metals varies in their forms and salts. Bioavailability of the metal from different compounds should always be considered because it is essential for induction and elicitation of allergic contact dermatitis. Metal allergy (in particular to Ni, Cr, Co and Hg) remains prevalent.

Abstract

Introduzione: La presenza dei metalli e dei loro derivati sui luoghi di lavoro e quindi il loro accumulo nell'ambiente è fonte di preoccupazione per il potenziale pericolo che essi rappresentano per la salute.

Obiettivi: Valutare necessariamente ed attentamente la potenziale esposizione della gran parte della popolazione ai metalli e ai loro prodotti.

Metodi: Diversi ricercatori hanno riscontrato grandi difficoltà tecniche nello svolgimento delle ricerche e ciò ha scoraggiato la realizzazione degli studi.
I diversi dati a disposizione sono stati ottenuti utilizzando condizioni sperimentali molto differenti tra di loro, rendendo difficile il confronto dei risultati.
La maggior parte dei dati disponibili in merito all'assorbimento percutaneo dei vari metalli, come nichel, cromo e cobalto, sia in vivo che in vitro, è stata pubblicata intorno agli anni '60 -'70 e i risultati non sono stati ottenuti usando metodi datati.

Risultati: Tra i vari effetti avversi causati dai metalli si riscontrano sia danni alla pelle, tra i quali irritazione, dermatite allergica da contatto, orticaria, granuloma, sia effetti tossici a livello sistemico.

Conclusioni: Nonostante le dimensioni del problema e le informazioni, ampiamente diffuse in letteratura, sugli effetti allergici e tossicologici di queste sostanze, sussiste una mancanza di dati sperimentali attendibili. Inoltre deve sempre essere considerata la biodisponibilità di ogni metallo, che varia in funzione dello stato e della forma, rappresentando un elemento essenziale nello sviluppo della dermatite allergica da contatto.
Resta comunque ragionevole affermare che l'allergia ai metalli (in particolare per Ni, Cr, Co e Hg) rappresenta la forma di allergia prevalente nei luoghi di lavoro.

Background

The presence of metals and their derivatives in the workplace and their accumulation in the general environment causes concern as a potential health hazard. In some cases they can exert toxic and/or carcinogenic effects by direct contact or systemic absorption through the skin. Data on allergic and toxicological effects of these substances, particularly those relating to the ability to penetrate the skin, are widely disseminated in literature and there have been attempts to summarize and organize them into reviews in order to make them easily accessible and understandable (1, 2). These reviews showed the lack of reliable experimental data on percutaneous penetration of metals. Several researchers found major technical difficulties that discouraged the carrying out of the studies. Moreover, results are obtained under very different experimental conditions, so comparison of results is difficult. A large part of the reported data on in vivo/in vitro percutaneous penetration of various metals such as nickel (Ni), Chromium (Cr) and Cobalt (Co) was published in

the '60s and '70s and the results were not obtained using up-to dated methods. More recently there have been attempts to standardize methods. In particular, The EDETOX project conducted within the European Union's Fifth Framework Programme in the years 2000-2004 represented an attempt to standardize methods (3).

In contrast, immunological investigations have historical origins and are constantly increasing. The immunological action of mercury (Hg) was revealed by Jadassohn more than 100 years ago, while Ni and Cr were soon recognized as a skin hazard with their widespread use in industry. After the Second World War a number of metals such as beryllium, platinum (Pt) and Co were identified as causal agents of allergies, which greatly increased the interest in dermal absorption of these compounds.

Besides the main areas relating to percutaneous penetration, skin allergies, local and systemic toxic effects, the use of skin appendages and secretions as matrixes for biological monitoring of metals attracts interest despite the lack of standardized methods (4).

Percutaneous penetration of metals

In general, percutaneous penetration of chemicals is of importance in occupational toxicology when the absorption through the skin contributes significantly to the body burden. Skin is usually an effective barrier to the absorption of metals as it functions as a reservoir. Percutaneous penetration of metals seems to be influenced by many factors such as oxidation, molecular weight, lipophilicity, reactivity and the nature of the metal compounds (salts). The permeability constant (Kp) expressed in cm/h is critical to compare the speed of penetration through the skin. However, it is a parameter ideally determined in steady state conditions which are difficult to reach during percutaneous penetration of metals due to their affinity to the stratum corneum. This makes it difficult to create predictive models.

Some metals penetrate the skin in no particular order and then form complete allergens binding epidermal proteins. Although in some cases (such as Ni) skin reactions can occur after oral uptake, generally the clinical manifestations of delayed hypersensitivity may be considered as an index of the ease with which the metal compound penetrates through the skin barrier. The most studied compounds are Ni and Cr, while Co has been studied primarily in occupational exposures.

Skin sensitization to Ni is the most frequent cause of allergy in industrialized countries. Despite the size of the problem, the knowledge about the penetration through the skin of this compound is inadequate to explain the rapid elicitation of eczema in sensitized individuals after simple contact with metal objects that contain it in limited quantities. In vivo and in vitro data indicated a tendency of increasing diffusivity of the more lipophilic Ni salts leading to believe that the preferred diffusion pathway was intercellular. However, other studies found conflicting results in which the molecular volume assumed greater importance than polarity (i.e. absorption mainly through the appendages) (5).

Ni in epidermis is bound in a reversible manner forming a reservoir. Its affinity for keratin influences percutaneous absorption so that from some salts the breakthrough time is considerable long (from 24 to 48 hours) (1). In particular, in vitro skin absorption of NiSO4 through human skin is very slow. Percutaneous penetration of 63Ni chloride was tested in a standardized in vitro system during the EDETOX project (Table 1).

Table 1: In vitro percutaneous penetration through human skin of 63Ni chloride and 57Co chloride from two different vehicles (6).

Compound	Vehicle	% after 24 h (M ± SD)	% in the epidermis (M ± SD)	% in the stratum corneum (M ± SD)
63Ni	water	0.23 ± 0.34	0.42 ± 0.55	50.33 ± 19.91
63Ni	artificial sweat	0.76 ± 1.21	0.34 ± 0.19	36.16 ± 9.30
57Co	water	1.04 ± 0.64	0.37 ± 0.20	27.62 ± 14.96
57Co	artificial sweat	3.30 ± 2.65	0.23 ± 0.14	41.30 ± 18.83

After 24 hours most of the metal was accumulated in the stratum corneum. Penetration through the skin was rather limited in accordance with literature. The artificial sweat increased the Ni penetration (6).
In vitro percutaneous penetration data do little to explain the apparent prompt penetration of Ni through the stratum corneum resulting in allergic contact dermatitis (ACD) (5). Ni affinity for the skin may play an important role in sensitization.

In the past, Cr was investigated in dermatology for its sensitizing action. Both the hexavalent form (Cr6+) and the trivalent (Cr3+) are potentially able to penetrate the skin. The different Cr3+salts have different skin absorption rates with a negligible penetration for Cr sulfate and nitrate. Cr6+ is mostly absorbed through the skin, being converted to Cr3+ up to a certain concentration. In a not recent in vitro dermal absorption study Samitz et al. (7) demonstrated a different penetration of Cr from various salts with a faster penetration of Cr6+ compared to Cr3+. In an in vitro study, skin penetration only occurred when Cr was applied as potassium dichromate, while it was only detectable in the skin when other salts (chloride and nitrate) were applied (8). The Cr penetration increased with increasing pH, probably due to a reduction of the barrier function. Significant differences were found in vivo and in vitro between Cr penetration through human and animal skin (1). An in vitro percutaneous penetration experiment through monkey skin carried out in 1998 in collaboration between the Unit of Occupational Medicine University of Siena and the Italian National Institute for Prevention and Safety at Work (ISPESL) showed a faster penetration of Cr6+ than Cr3+ with an average Kp of 0.60 x 10-3 and 0.16 x 10-3 cm/h respectively (not published data).

The absorption of Co through the dermal route was demonstrated on human volunteers and confirmed in experiments in vitro on human skin with percutaneous penetration of ions derived from metal oxidation by sweat (9). In the aforementioned study conducted under the project EDETOX (6) the Co behaviour was similar to Ni, but with a percutaneous penetration about 5 times greater (Table 1).

For mercurial compounds the skin is considered an important route of absorption so as to be marked with a skin notation in the list of ACGIH limits and other governmental and international Agencies. All Hg forms are absorbed through the skin with the organic compounds, the metal vapors and some lipophilic salts such as $HgCl_2$ more easily absorbable. The absorption of the metallic Hg through the skin of the volunteers forearm was measured for a period ranging from 0.25 to 0.75 hours (11). The Kp ranged from 0.61 to 2.41 cm/h. About half of the compound absorbed in the exposed areas was eliminated in subsequent desquamation in 5-6 weeks, while the remainder went into circulation in the course of several days with a peak one week after exposure. A study conducted in a multicenter Italian research compared in vitro percutaneous penetration through human skin of Hg from an aqueous and a solid medium to test the bioavailability of the metal in two different conditions, demonstrating the absence of absorption from solid carrier in agreement with what reported in literature for other compounds (12). Therefore dermal contamination with soil containing Hg does not seem a major source of danger to public health. Percutaneous absorption of Hg from the aqueous solution appeared rather quick and relevant. The cumulative percutaneous penetration was higher in cells where the solution was applied at higher concentrations. However, increases in the percentages of passage were significantly lower in cells where the higher concentration was applied and Kp values were also lower. This could be attributed to the formation of a reservoir due to the high affinity for the stratum corneum of the heavy metals.

Lipophilic organic compounds of lead (Pb) easily penetrate the skin barrier, while the inorganic form is poorly absorbed because of its ability to bind to proteins. In particular it has not been demonstrated in vitro penetration of Pb oxides neither through human skin nor in animal models (13). However it was demonstrated that the application of Pb nitrate on forearm of human volunteers causes excretion of high concentrations of the metal in the sweat of the contralateral limb, in the absence of an increase of blood lead (14). The authors concluded that absorption should take place rapidly through the sweat gland ducts and more slowly through epidermis. Furthermore, because of a poor affinity for red blood cells, Pb penetrated through the skin would be distributed almost exclusively in the intercellular fluid. This was not confirmed by the aforementioned research in collaboration between the Unit of Occupational Medicine University of Siena and ISPESL, where in vitro tests through monkey skin did not show a Pb penetration from crystal dust grinding.

Contact dermatitis

Contact dermatitis is the most important clinical manifestation of skin exposure to metals. Metal allergy (in particular to Ni, Cr, Co and Hg) remains prevalent, the pattern of exposure changing over the decades, mainly as a result of regulatory interventions and increased work hygiene (15). Some substances are potent skin sensitizers in animal tests and patch tests in humans. However, often these reactions are not clinically relevant because of the lack of exposure in workplaces and general environment. A genetic predisposition in metal allergy has been suspected. Null mutations in the filaggrin gene complex were found to be associated with Ni allergy and dermatitis (15).

Bioavailability of metals varies in their forms and salts. Bioavailability of different metal compounds should always be considered because it is essential for induction and elicitation of ACD. This explains how the elementary Cr is not dangerous, while the chromates soluble in water are a very common cause of ACD and why some precious metals are not dangerous, while their salts are potent skin sensitizers.

Nickel

Ni at the moment represents the most important cause of ACD. ACD by Ni is a global socio-economic problem of vast proportions affecting 10-20% of European women. About 40% of sensitized subjects who developed dermatitis may experience detrimental socioeconomic consequences such as sick leave and job loss. Usually sensitization occurs by exposure to Ni derived from releasing consumer items such as jewelry, keys, buttons, watches, zippers, piercings, etc.. Thus in 1994 the EC decided to limit the use of Ni in the objects used in direct and prolonged contact with skin (16). Professional exposure to Ni in occupations such as hairdressers, metal workers, locksmiths and cashiers can result in ACD (17, 18). Shah et al. (19) in a survey of 368 Ni sensitive subjects suffering from ACD found a relevant occupational exposure to Ni which occurred in 22.8% of patients.

Chromium

Cr salts in powder or solution form are known to cause skin irritation, nasal perforations and ulcers. However, skin reactions to wet cement relate to the high pH (~ 12) rather than to the Cr content.

Both Cr^{3+} and Cr^{6+} can cause allergies. The dichromate ACD from contact with cement is a classic occupational disease causing job loss and long-term unemployment. The risk is related more to the soluble chromate concentration in water than to the total Cr content. In the Northern European Countries the addition of iron sulphate to inactivate the chrome content in the cement reduced the incidence of ACD (20).

Cobalt

The industrial use of hard metal containing Co results in irritant contact dermatitis.

Co sensitization is common and usually associated with that to Cr or Ni. Ni is often contaminated by Co and cement contains both Cr and Co. As a result, this association can probably be interpreted as due to the combined exposure to these metals and not as a cross-sensitization.

Mercury

Many mercurial compounds (in particular $HgCl_2$) are skin irritants especially when occlusion conditions occur.

Generally, skin sensitivity to mercurial compounds has little clinical significance since it may derive from the presence of thimerosal in vaccines and dental amalgams used in the recent past.

Platinum

ACD by Pt released from jewelry is rare. Industrial exposure to chloroplatinates can result in ACD and contact urticaria, as well as severe asthma.

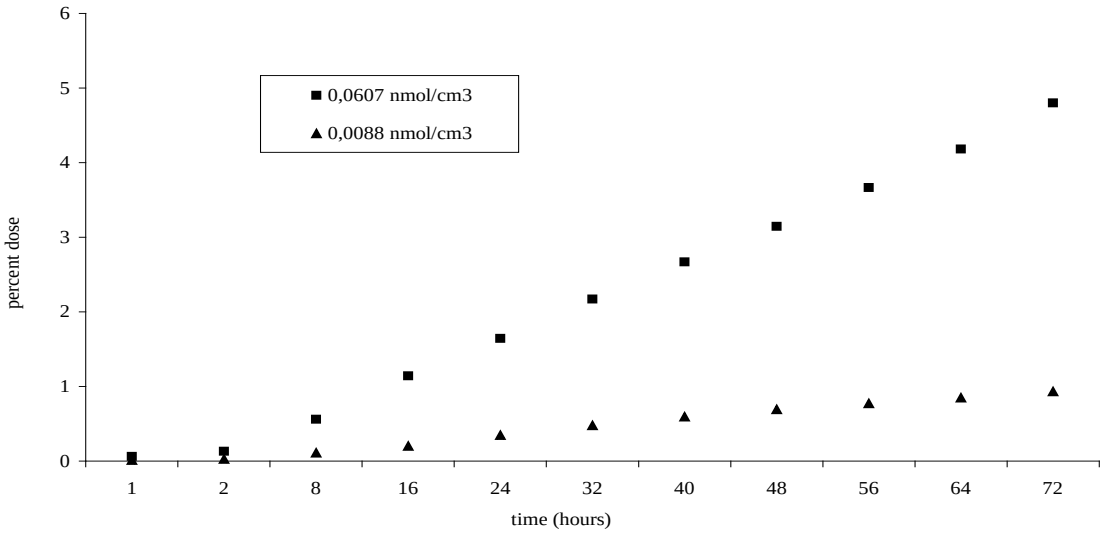
Rhodium

In experimental animals, Rhodium has proven to be a powerful skin sensitizer. In literature there are reports of individual cases of ACD from rhodium salts in jewelry manufacture and dental material.

Palladium

Palladium (Pd) may be contained in jewelry and dental fillings. Pd chloride is a potent skin sensitizer in laboratory animals. Sensitization to Pd salts is not uncommon, but its clinical significance is unclear given also the frequent presence of a concurrent positive Ni.

Figure 1: In vitro percutaneous penetration through human skin of 203HgCl2 applied in two different concentrations in an acqueous vehicle (12).



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