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Metals in cosmetics: An *a posteriori* safety evaluation

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ABSTRACT

According to EU Regulation No. 1223/2009/CE cosmetic products for daily use can contain '*technically unavoidable traces*' of metals. This definition is too vague. Authorities should set well-defined limits, considering the risks associated with metal contamination of personal care products (PCPs).

This paper characterizes the risk arising from a number of metals (antimony, arsenic, cadmium, cobalt, chromium, mercury, nickel, lead) that may occur in 'unavoidable traces" in raw materials and, consequently, in PCPs. A 'worst case scenario' was adopted, based on the following assumptions: (i) the individual ingredients contained the maximum amount in traces allowed for each metal; (ii) the hypothetical PCP was produced exclusively with that single ingredient; (iii) when absorption through the skin was not known, data related to oral absorption were used. Risk characterization was performed calculating the Systemic Exposure Dosage (SED) and the Margin of Safety (MoS = NOAEL or $BMDL_{10}$/SED). Exposure to the allegedly 'technically unavoidable' maximum amounts of metals in cosmetic ingredients resulted in MoSs exceeding 100 (safety threshold) with one exception. This suggests that the availability of experimental dermal absorption rates could enable significant improvement in MoS, thus increasing safety levels. Although results are reassuring, the authors recommend minimization of contamination, according to the state of the art of manufacturing methods.

1. Introduction

Humans are exposed to naturally occurring metals released by the environment *via* a broad range of routes every day. Atmospheric emissions tend to be of greatest concern in terms of human exposure and health, both because of the amount of metals involved and the widespread dispersion (Harmens et al., 2010).

However, other less obvious sources of exposure have to be considered, including the use of cosmetic products. Indeed, metal traces can be detected in most cosmetic products as impurities, leading to direct exposure of a large number of individuals. The ever improving sensitivity of analytical methods enables the detection of increasingly lower trace levels. Consequently, metal traces are more frequently and easily detected in cosmetic products, even when they are manufactured according to good manufacturing practices (GMP). Regulation No. 1223/2009/CE (EC, 2009) allows the presence of metals in finished products in 'small quantities', defined as '*technically unavoidable traces*', subject to compliance with GMP and, above all, on condition that marketed cosmetic products are safe for human health under normal or reasonably foreseeable conditions of use (Art. 3) (EC, 2009). The final responsibility for ensuring the safety and regulatory compliance of a cosmetic product rests with the organization responsible for placing the product on the market (i.e. manufacturer, distributor and/or importer).

However, the definition "*technically unavoidable traces*" is vague, subject to interpretation and highly dependent on the technology used for production. Even when such technology complies with GMP in the EU, the issue of products coming from extra-European countries, where GMP are not mandatory, remains. Therefore, appropriate management of 'traces of metals' in cosmetic products is required. Indeed, cosmetic industries and consumers alike expect European country authorities to set well-defined limits, based on assessment of actual exposure, so that they can establish the risk associated with contaminated personal care products (PCPs).

2. Concept of risk analysis

Risk analysis is a complex process that includes three key steps: risk assessment, risk management and risk communication. Risk assessment provides the scientific basis on which the whole risk analysis rests. It follows an international, well accepted process

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that includes 4 steps: (1) hazard identification, (2) hazard characterization, (3) exposure assessment and (4) risk characterization, which assesses the likelihood of adverse health effects occurring under specified conditions of exposure. The procedure is well documented in the European Directive 67/548/EEC (EC, 1993; ECHA, 2013) and based upon the principles and practice of the risk assessment process developed within the World Health Organization, the United Nations Environment Programme and the International Labour Organization's (WHO/UNEP/ILO) International Program on Chemical Safety revised in 2004 (WHO, 2004).

3. Safety assessement of personal care ingredients and products

Most PCPs enter into contact with human skin, occasionally resulting in local adverse effects. In addition, depending on their chemical and physical properties, skin penetration may occur leading to human systemic exposure. The safety of PCPs is regulated under cosmetic and/or pharmaceutical regulations within the EU, under CFR – Code of Federal Regulations Title 21 – part 700 in the US (FDA) and under the Standard for Cosmetics; Ministry of Health and Welfare Notification No. 331 of 2000 in Japan.

Cosmetic formulators have to be aware of the dual approach in Europe towards the safety of cosmetic ingredients, which involves both the Scientific Committee on Consumer Safety (SCCS) for some categories of ingredients (preservatives, UV filters, hair dyes, etc.) and an individual safety evaluation performed by product manufacturers on the ingredients that are not subject to any regulatory restrictions. Under the old Cosmetics Directive 76/768/EEC (EC, 1976), this safety assessment followed the principles described in the earlier 7th edition (SCCS, 2010a,b) of the 'Notes of Guidance for Testing of Cosmetic Ingredients and Their Safety Evaluation' by SCCS, recently revised in the 8th edition (SCCS, 2012). The new Cosmetics Regulation 1223/2009 (EC, 2009) did not introduce any further requirements, but it defines the format of the Cosmetic Product Safety Report (CPSR) (EC, 2009).

The safety of PCPs is estimated according to the safety of their ingredients, starting from the principle that interaction among ingredients is not relevant. The toxicological profile of individual ingredients should address at least the endpoints of acute toxicity, skin and eye irritation, skin sensitization, as well as photo-induced toxicity in the case of UV absorption. Other data (including toxicokinetics, genotoxicity, repeated toxicity and reproductive toxicity studies) can be requested as well. The non clinical studies designed to evaluate the safety of an ingredient should be carried out in compliance with good laboratory practice (GLP) according to the EU legislation (EC, 2009) (Art. 10), by using non animal methods, which are available and adopted as OECD Test Guidelines at least for local toxicity end-points (OECD). In addition, other already available *in vitro* and *in vivo* toxicological data, obtained for the registration of chemicals within other legislative frameworks, as well as results from *in silico* approaches, like Quantitative Structure Activity Relationships (QSAR), and from the application of read-across analysis of structurally related compounds, combined with any available information from dermatological tests, post-market surveillance, scientific literature data, can be used in a Weight of Evidence (WoE) approach.

The risk characterization of a PCP is the assessment of the probability of causing damage to human health at the actual (or foreseeable) level of exposure; the level of risk can be expressed as Margin of Safety (MoS), that is the magnitude by which the NOAEL of the critical toxic effect exceeds the estimated exposure dose, calculated according to the formula

$$MoS = NOAEL/SED$$

where NOAEL is the No Observed Adverse Effect Level and SED is the Systemic Exposure Dosage.

Based on past experience of other scientific committees operating internationally, SCCS decided that MoS should reach a value of 100 to suggest that the use of the ingredient in the PCP is not associated with significant risk for human health. A NOAEL derived from a 90-day oral study in rodents or dogs is considered adequate (considering the oral route as a worst case with respect to the dermal route), but also data from shorter studies (28 days) as well as a LOAEL (Lowest Observed Adverse Effect Level) value can be used, after application of correction factors (SCCS, 2010a,b, 2012).

The Lowest Benchmark Dose (BMDL) is proposed as an alternative to the classical NOAEL values (MoS = BMDL/SED). The BMDL is based on a mathematical model fitted to the experimental data within the observable range; it estimates the dose that causes a low, but measurable response (the benchmark response: BMR) typically chosen at 10% incidence (BMDL10) above the control (SCCS, 2012). It is considered a more robust Point of Departure (PoD) to derive health-based values from, since it is not dependent on the experimental design as the NOAEL is.

Conversely, the SED of a cosmetic ingredient is the amount expected to enter the blood stream daily (and therefore be systemically available) per kg body weight, assuming, for risk characterization purposes, an average human body weight of 60 kg for an adult.

Most cosmetic products are applied topically. Therefore systemic availability will strongly depend on the dermal absorption of the compound (SCCS, 2012). The SCCS was the first body to introduce the SED concept systematically, referring the risk to systemic effects of the actually bioavailable dose rather than to external exposure (SCCS, 2010a,b).

When calculating the SED, the SCCS takes the product type into account. When the product is topically applied onto the skin surface (cm^2), it also considers the area involved (total body, hands, head, etc.), the frequency of application (daily, weekly, monthly) and dermal absorption of the test substance reported in $\mu g/cm^2$. Alternatively, the dermal absorption can be expressed as a percentage of the amount of substance applied: in this case the SCCS utilizes product type, estimated daily amount applied (g), relative amount applied (mg/kg b.w./day), retention factor (rinsing off, dilution), calculated daily exposure (g/day) and the calculated relative daily exposure (mg/kg b.w./day).

Dermal absorption data is crucial in the safety evaluation of a cosmetic product. The OECD Test Guideline No. 428 (OECD) describes the possibility of obtaining such data with *in vitro* methods, making it suitable for cosmetic ingredients/products also under the new Regulation. Indeed, the SCCS has provided specific guidance on this topic in its opinion 'Basic criteria for the *in vitro* assessment of dermal absorption of cosmetic ingredient' (SCCS, 2010a,b).

The SCCS has discussed the issue of cutaneous absorption in depth, as well as the problem of having to extrapolate from absorption values obtained by oral administration of a chemical (whenever available). If there is evidence suggesting poor oral bioavailability, for example when the substance is a poorly soluble particulate or in form of insoluble oxides (e.g. Cr_2O_3), it may be more appropriate to assume that only 10% of the administered dose is systemically available (IGHRC, 2006). However a specific SCCS guidance document on this issue is in preparation.

Dermal absorption data can also provide information on the need for further testing. For instance, testing for systemic toxicity is only necessary if the ingredient penetrates into the body following dermal, oral, or inhalation exposure (Adler et al., 2011).

Alternative approaches to the MoS calculation, like the Threshold of Toxicological Concern (TTC), have been proposed for the