Heavy metal content in cosmetic products: a comparative review on permissible levels in global regulatory requirements and available analytical tests

Modddaresi, M; Yu, J

Personal Care Regulatory Ltd, St John Innovation Centre, Cambridge, UK

Abstract

Heavy metals are generally not permitted to be added individually in cosmetic products. However, they are naturally occurring elements and present in mineral and natural ingredients like pigments and herbal extracts. Heavy metals are identified to have potential health risks like carcinogenic and mutagen potency. Hence, evaluating potential risk of unavoidable impurities can be crucial for consumers' health. The aim of this review is to have a comparative review on major global cosmetic markets (USA, Canada, EU, UK and China) on limitation and evaluation of heavy metal contamination in cosmetic products to ensure finished products' safety.

For this comparative study, two types of regulatory systems: self-regulatory and obligatory registration were chosen. For markets with self-regulatory system, United Kingdom, Canada and European Union with mandatory products' notification and United States as a market with non-mandatory notification were chosen. For market with obligatory registration China and India were considered for this comparison. In addition to obligatory regulations, horizontal regulatory regulation that may affect evaluation of heavy metal contamination in cosmetic products were investigated. Furthermore, acceptable analytical tests with relevant limit of detection used to evaluate heavy metals content have been reviewed.

Based on the EU and UK Regulation, traces of unavoidable impurities under Good Manufacturing Practice (GMP) are permitted in cosmetic products. While there is no specific limit set in the regulation for unavailable impurities, the responsibility of final products' safety is on shoulders of qualified safety assessors. Even though there are substantial guidelines on evaluation of systemic dosage exposure for potential carcinogen materials, the decision on threshold of concern for such impurities is not an easy process. In some of the EU member of states like Germany, a set values for "technically avoidable" metal content to be used in cosmetics was considered and consequently a monitoring scheme in place to review the levels for finished products on the market. In the UK, the new scientific committee under supervision of Office for Product Safety and Standards (OPSS) is yet to comment on this matter and still follows the same guideline of the EU regulation 1223, 2009. In addition, horizontal regulations in the EU and UK which can impact restriction of heavy metals in finished products. In both regulations, there is a list of approved colourants (Annex IV) with certain restriction for impurities of colorants (Annex IV). Above all, for placing any chemical ingredients on the market compliance with Regulation (EC) No 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) and the UK counterpart (UK REACH) is an obligation. Under REACH, articles (that is, finished products) cannot be sold if they exceed limits for certain chemical substances, such as heavy metals.

In the United States, Food and Drug Administration (FDA) addresses some heavy metals as cosmetic ingredients or impurities in colour additives while Health Canada has a guideline on heavy metal impurities in cosmetic products. In none of the countries under self-regulatory system, there is a specific approved method for evaluation of heavy metal contamination in finished cosmetic products, though ISO 21392:2021 is considered as an acceptable standard for the market**.**

In China, Chinese safety and Technical standard 2015 has a set testing and approved method for evaluating cosmetic products' impurities before being placed on the market. In India, the Drugs & Cosmetics Act 1940 and Drugs & Cosmetics Rules 1945 which recently replaced by Cosmetic rules 2020 has specific set limit for heavy metals only for synthetic organic and natural colours.

In conclusion, after evaluation of definition of heavy metals in different regulatory systems and discrepancies on limits it can be concluded that there is a lack of harmonisation which can lead to confusion for authorities and respectively ingredients' manufacturers. The different approach on setting a standard for heavy metals contamination which may be rooted either in political issues or difference in risk assessment approach (hazard identification versus risk assessment) may lead to serious impacts

on consumers' trust in safety of cosmetic products. This lack of harmonisation can also impact manufacturers and suppliers of ingredients in global supply chain connected internationally.

1. Introduction

Heavy metals are known to pose potential health risks to the human body. The contamination of cosmetic products with these substances is therefore a crucial aspect of consumer safety, especially given the growing popularity of such products as part of routine body care. Although heavy metals are encountered in a variety of naturally occurring sources, their presence as impurities in cosmetic products has attracted increasing attention over the past decade given their possible influence on safety outcomes. It is important to appreciate that heavy metal impurities cannot be avoided entirely, due to their ubiquitous nature and natural origins, but they should be kept to a minimum whenever feasible to help ensure product safety.

The term 'cosmetic products' covers a wide range of different personal care products and its definition varies in different jurisdictions, but generally refers to products applied topically on the body. Irrespective of differences in classification, the ultimate aim of every regulatory system, and self-regulatory or obligatory registration, is to ensure the safety of end consumers while using these products. Cosmetic products generally include multiple ingredients, which may each contain different impurities at different levels depending on their origin, but overall exposure in the finished product is the most relevant aspect for consumer safety.

1.1 Heavy metals and their harmful effects

While there is no clear consensus on the exact definition of a heavy metal, the term is generally applied to metals with relatively high densities (>5 g/cm^3), atomic weights, or atomic numbers. They are primarily present in areas of the periodic table defined by metallic characteristics, including the ability to form salts. Examples of heavy metals relevant to this discussion include lead, cadmium, nickel, mercury, antimony and arsenic. Some of these, such as lead and arsenic, are usually regarded as impurities, whereas others (including cadmium, nickel and mercury) may be intentionally present in colouring agents or preservatives, as well as being potential contaminants. These metals can all be found in nature and are quintessential for metabolic reactions in plants (Dorne et al., 2011), but their accumulation can adversely impact the environment as well as living organisms (Järup, 2003).

For example, nickel is sometimes used as an ingredient in cosmetic products but is well known for its association with allergic chronic dermatitis; and although mercury is rarely found in cosmetic products, its toxicity is clearly established and it has been identified at significant levels in skin lightening cream (Tamara & Attard, 2022). As already mentioned, it is impossible to completely avoid the presence of some degree of contamination in consumer products, so it is therefore crucial to understand the toxicological effects of each potential heavy metal impurity along with the relevant regulatory requirements for cosmetic products.

Human skin normally acts as an effective defensive system and barrier, providing protection against these substances, and inflammatory reactions are usually sufficient to eliminate foreign particles such as absorbed heavy metals. However, long-term exposure may cause heavy metals to accumulate in the epidermal tissue, and their relevant penetration into the skin is similar to that seen for inorganic compounds (Guy et al., 1999).

1.1.1 Lead

Lead (Pb) is a metallic element that is denser than most common materials, and which is known to be neurotoxic, nephrotoxic and hepatotoxic (Patrick, 2006; Karri et al., 2016). The available data also suggest that lead might be a reproductive toxin (USHHS & USCFSAN, 2016), and there is some evidence of carcinogenicity to humans (Sprinkle, 1995). In terms of cosmetics, certain critical product groups have relatively high levels of lead contamination—including makeup powder, blusher, eye shadow and kajal (including eyelid liner and eyeliner)—as well as theatre, fan and carnival makeup (BVL, 2017). However, given the well-established hazardous nature of lead, regulatory authorities have defined various upper limits for cosmetic products.

Lead and its compounds are prohibited in cosmetic products in the EU according to Annex II, item 289 of the EU's Regulations for Cosmetic Products (EU 1223/2009) and are also restricted in Annex XVII to the European Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH). The German Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (BVL) has established a technically unavoidable limit of 2 mg/kg for all products. This value was derived from the 90th percentile of products evaluated under the German Monitoring Scheme, where a total of 1,735 samples covering a wide range of cosmetic products were analysed for heavy metal content (BVL, 2017). The US Food and Drug Administration (FDA) has also established a maximum level for lead as an impurity in cosmetics, of 10 ppm. This applies to all cosmetic lip products (e.g., lipstick, lip gloss and lip liner) and externally applied cosmetics (e.g., eye shadow, blusher, shampoo and body lotion) marketed in the United States (USHHS & USCFSAN, 2016). In Canada, similarly to the EU, lead and its compounds are prohibited in cosmetic products as specified in the Cosmetic Ingredient Hotlist. However, for products licensed under the monograph stream of the Natural Health Product Regulations made under the Food and Drugs Act, there is a limit for lead impurities of 10 ppm in products applied to the skin (Natural Health Products Directorate, 2007). In China, where testing for harmful substances in finished cosmetic products is mandatory, lead must not exceed a level of 10 mg/kg (10 ppm). In India, according to the permitted Synthetic Organic Colours and Natural Organic Colours used in the Cosmetic, such products must not contain more than 20 mg/kg lead. In addition, the use of lead in colourants is prohibited.

1.1.2 Cadmium

Cadmium (Cd) is an example of a heavy metal that can be either an ingredient or a contaminant. It is widely employed to colour cosmetics, in particular using its various coloured salts that range from yellow to orange. The major safety concern with cadmium is its potential systemic toxicity, which mainly affects the skeletal, metabolic, respiratory, reproductive and renal systems (Rebelo, 2016; Bocca et al., 2007; Mahurpawar, 2015). Under the EU Classification, Labelling and Packaging of Substances and Mixtures (CLP) regulation, cadmium has classifications of H341 (suspected of causing genetic defects) and H350 (may cause cancer). Since it is classed as a carcinogenic, mutagenic and reprotoxic (CMR) substance, cadmium and its compounds are prohibited in cosmetic products in the European Union, as listed in Annex II, item 68 of EU regulation 1223/2009, and are also restricted in Annex XVII to the REACH. In the study mentioned above, the German BVL established that the 90th percentile for cadmium in cosmetic products is significantly below 0.1 mg/kg. As such, it was proposed that 0.1 mg/kg should be considered as the technically unavoidable limit for all products, including toothpaste (BVL, 2017). Cadmium is also classified as a human carcinogen in the United States, by the National Institute for Occupational Safety and Health (NIOSH). In Canada, cadmium and its compounds are prohibited in cosmetic products as listed on the Cosmetic Ingredient Hotlist, again in line with EU regulations. In China, cadmium must not exceed 5 mg/kg in finished cosmetic products.

1.1.3 Arsenic

Arsenic (As) has varying health effects in humans depending on the compound and form. For example, metallic arsenic is not absorbed from the gastrointestinal tract and possesses no known adverse health effects (Health Canada, 2006). In contrast, inorganic arsenic is carcinogenic (Edward, 2000), and it has been reported that systemic arsenic may lead to cancer and vascular diseases (Bhattacharjee, 2013; Gibb et al., 2011). Given this carcinogenicity, arsenic and its compounds are prohibited in cosmetic products in the EU—as listed in Annex II, item 43 of EU regulation 1223/2009—and arsenic compounds are also restricted in Annex XVII to the REACH. In the German study referred to previously, the 90th percentile of arsenic in cosmetic products was between 0.5 and 0.9 mg/kg, even taking into account the specific case of toothpastes. The BVL therefore considers levels above 0.5 mg/kg to be technically avoidable with good manufacturing practice (BVL, 2017). In Canada, arsenic and its compounds are prohibited in cosmetic products (as specified in the Cosmetic Ingredient Hotlist), again in agreement with the EU's RCP. The US FDA has established a maximum level of 3 ppm for arsenic as an impurity in cosmetic additives. In China, arsenic must not exceed 2 mg/kg in finished cosmetic products, and the same limit applies India (calculated as As_2O_3), according to the permitted Synthetic Organic Colours and Natural Organic Colours used in the Cosmetic. This regulation also prohibits the use of arsenic compounds for colouring cosmetics.

1.1.4 Mercury

Mercury (Hg) is widely used in cosmetic formulations. Inorganic mercury is known for its skin lightening properties, and organic mercury (methylmercury) is widely used as a preservative in mascaras. Mercury compounds may cause allergic reactions, skin irritation or neurological adverse effects. Clinical symptoms of overexposure to mercury include tremors, weakness, memory loss, dermatitis and impaired kidney function. The form of mercury involved typically determines the specific symptoms (Hostynek, 2001), and in terms of toxicity, organic forms of mercury are of greater concern than inorganic forms. Under the CLP, mercury has a harmonised classification of H360D (may damage the unborn child), and given this reproductive toxicity, mercury and its compounds are generally prohibited in cosmetic products in the EU (Annex II, item 221 of EU regulation 1223/2009). However, because mercury can be an effective preservative in eye products, its presence is allowed in cosmetic products in exceptional cases, as defined in Annex V of the regulation restricting the use of preservatives. Mercury compounds are also restricted in the REACH (Annex XVII). In the German BVL study, it was established that the 90th percentile for mercury in cosmetic products is significantly below 0.1 mg/kg, so this was specified as the technically unavoidable limit for all products, including toothpaste (BVL, 2017). In Canada, mercury and its compounds are again found on the Cosmetic Ingredient Hotlist, prohibiting their use in cosmetic products. In the United States, there is a limit of 1 ppm mercury for colour additives, and while it is generally prohibited in cosmetic products, some eye products may contain small amounts of preservatives with mercury (e.g., thimerosal). In such cases, the mercury content must not exceed 65 ppm in the finished product, with the caveat that no alternative safe and effective preservative must be available. In China, there is a limit of 1 mg/kg mercury in finished cosmetic products, and in India, unintentional mercury should likewise not exceed 1 ppm in most finished cosmetic products. For cosmetics intended for use only in the eye area, a higher level of mercury is permissible, but it must not exceed 70 ppm (calculated as the metal, as a preservative).

1.1.5 Antimony

Antimony (Sb) does not have a harmonised classification under the EU CLP, but some notifiers have classified it as H351 (suspected of causing cancer) and H360 (may damage fertility or the unborn child). Furthermore, overexposure to antimony and its compounds can adversely affect the skin, lungs, cardiovascular system and liver. In view of their hazardous properties, these substances are prohibited in cosmetic products in the EU (as specified in Annex II, item 40 of EU regulation 1223/2009). Antimony compounds are also restricted in Annex XVII to the REACH. The study by the German BVL found that the 90th percentile of antimony was below 0.5 mg/kg in all product groups. This regulator therefore considers levels above 0.5 mg/kg to be technically avoidable. In Canada, antimony and its compounds are prohibited in cosmetic products, as for the other examples above, and are again included on the Cosmetic Ingredient Hotlist. There are no specific regulations relating to antimony content of such products in China or India.

1.1.6 Summary of restrictions on heavy metal impurities

In general, heavy metals and their compounds are prohibited impurities in cosmetic products due to their established toxicology and the associated risks. For the examples discussed here—lead, arsenic, cadmium, mercury and antimony—extensive studies have characterised the hazardous properties of each, meaning that these heavy metals are restricted in cosmetic products by the representative regulatory bodies named above. However, due to the fact that heavy metals are naturally occurring substances, it is appreciated that they cannot be entirely eliminated from cosmetic products and that some level of contamination is technically unavoidable. Given this, alongside the fact that heavy metals can sometimes be constituents of functional ingredients, regulatory bodies have established various prohibitions and restrictions relating to them. Table 1 summarises the acceptable limits for heavy metals in cosmetic products as defined by the relevant regulations in various localities, as well as detailing the different horizontal regulations that can be used as a reference when evaluating the heavy metal content of cosmetic products.

Table 1: Limits on heavy metals in different regional cosmetic regulations, and horizontal regulations.

Regulations \ Heavy Metals	Lead (Pb)	Arsenic (As)	Cadmium (Cd)	Mercury (Hg)	Antimony (Sb)
EU Cosmetic regulation EC 1223/2009[1]	Prohibited, Annex II/ 289	Prohibited, Annex II/ 43	Prohibited, Annex II/ 68	Prohibited, Annex II/ 221	Prohibited, Annex II/ 40
EU REACH[2]	Controlled, Annex XVII entry 63	Controlled, Annex XVII entry 19	Controlled, Annex XVII entry 23	Controlled, Annex XVII entry 18	Not controlled as Antimony on its own.
German BVL Technically Unavoidable Limit[3]	2.0 mg/kg in general products, 0.5 mg/kg in toothpaste	0.5 mg/kg in general products and toothpaste	0.1 mg/kg in general products and toothpaste	0.1 mg/kg in general products and toothpaste	0.5 mg/kg in general products and toothpaste
Canada Cosmetic Ingredient Hotlist[4]	Prohibited	Prohibited	Prohibited	Prohibited	Prohibited
US FDA proposed limits in cosmetic products[5]	1. Maximum level of 10 mg/kg Lead as an impurity in cosmetics. 2. Not more than 20 mg/kg in colour additives.	Not more than 3 mg/kg in colour additives.	-	1. Allowed in cosmetics only as preservatives in eye area products. 2. Must not exceed 65 ppm in the finished product. 3. Only if no other effective and safe preservative is available. 4. Not more than 1 mg/kg in colour additives.	-
China's Safety & Technical Standard 2015[6]	Must not exceed 10 mg/kg in finished product.	Must not exceed 2 mg/kg in finished product.	Must not exceed 5 mg/kg in finished product.	Must not exceed 1 mg/kg in finished product.	-
India's Cosmetic Rules 2020[7]	1. Permitted Synthetic Organic colours and Natural Organic Colours used in the Cosmetic shall not contain more than 2 mg/kg Lead calculated as Lead. 2. The use of Lead compounds for the purpose of colouring cosmetics is prohibited.	1. Permitted Synthetic Organic colours and Natural Organic Colours used in the Cosmetic shall not contain more than 2 mg/kg Arsenic calculated as Arsenic Trioxide. 2. The use of Arsenic compounds for the purpose of colouring cosmetics is prohibited.	-	1. In cosmetics intended for use only in the area of eye, the level of mercury shall not exceed seventy mg/kg of mercury, calculated as the metal, as a preservative. 2. In other finished cosmetic products, unintentional mercury shall not exceed 1 mg/kg.	-

[1] Consolidated text: Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products, 02009R1223 — EN — 01.03.2022 — 030.002

[2] European Chemical Agency, Substances restricted under REACH, Annex XVII to REACH. Available at https://echa.europa.eu/substances-restricted-under-reach (Last accessed on 06/07/2022)

[3] BVL (2017). Technically avoidable heavy metal contents in cosmetics. Journal of Consumer Protection and Food Safety, 12:51–53.

[4] Cosmetic Ingredient Hotlist. Available at https://www.canada.ca/en/health-canada/services/consumer-product-safety/cosmetics/cosmetic-ingredient-hotlist-prohibited-restricted-ingredients/hotlist.html (Last accessed on 06/07/2022).

[5] FDA's Testing of Cosmetics for Arsenic, Cadmium, Chromium, Cobalt, Lead, Mercury, and Nickel Content. Available at https://www.fda.gov/cosmetics/potential-contaminants-cosmetics/fdas-testing-cosmetics-arsenic-cadmium-chromium-cobalt-lead-mercury-and-nickel-content (Last accessed on 06/07/2022)

[6] China's Safety & Technical Standard for Cosmetics 2015

[7] India's Cosmetics Rules, 2020

2. Cosmetic testing for trace heavy metals

A limited number of analytical methods are available for the accurate detection and quantification of heavy metals in cosmetic finished products or their raw materials. The latest guidance note from the Scientific Committee on Consumer Safety (SCCS 11th Revision, 1628/21) on health, environmental and emerging risk, published in 2021, documents various analytical methods including HPLC-PDA (HPLC with photometric diode array detection), LC-MS/GC-MS, NMR spectroscopy, and others, using reference standards with documented purity. These methods were recommended to identify impurities in ingredients, but no specific recommendation is made regarding the acceptable limit of non-CMR impurities in cosmetic products. The only emphasis in the SCCS document is the employment of validated methods using reference standards with documented purities.

The China Safety & Technical Standard 2015 has stablished certain analytical methods for each individual heavy metals of concern in the regulation:

Mercury, Arsenic - hydride generation atomic fluorescence spectrometry,
Lead - Graphite furnace atomic absorption spectrometry
Cadmium - flame atomic absorption spectrophotometry

Even though FDA has not defined any approved method, but has published a FDA-validated total dissolution method, using hydrofluoric acid. In the published FDA validated method to survey the market, arsenic, cadmium, chromium, cobalt, lead, and nickel was analysed by inductively coupled plasma-mass spectrometry and for mercury by cold vapor atomic fluorescence spectrometry. The methods used to determine the elements were tested for validity by using standard reference materials with matrices similar to the cosmetic types (Hepp et al 2014).

A related technical report from International Organization for Standardization (ISO), published in 2014 (ISO/TR 17276:2014), addresses the most common analytical approaches used for screening and measurement of heavy metals, introducing those of general interest at both raw material and finished product level. Following its release, this report became perhaps the most important of only a few existing documents outlining this type of analysis. It contained useful general guidelines about the different approaches to heavy metal determination, but lacked comprehensive details of operational procedures and data on the comparative performance of different methods. Thus, the feasibility and implementation of the methods described were subject to variability depending on the performance of individual laboratories. In the context of growing interest and demand around heavy metal analysis of cosmetic products and their raw materials, ISO issued a new standard in 2021. This updated document (ISO 21392:2021) details the use of inductively coupled plasma mass spectrometry (ICP-MS), an analytical technique with high sensitivity that allows determination of trace metals at levels down to 0.02 mg/kg (MILESTONE, 2021). This new standardised method offers high sensitivity for the quantification of heavy metals in cosmetic raw materials and finished products. Contaminant levels in the finished goods can then inform safety evaluations, giving manufacturers and consumers alike a better understanding of whether the products are safe to use.

3. Discussion

Although the need to restrict the heavy metal content of consumer products at the regulatory level is clearly understood, there is little agreement on permissible safe limits, together with a notable lack of consistency in monitoring outcomes. For example, in the UK and EU, there is a general prohibition on heavy metals with established toxicity with defined limits only for certain allowed ingredients (in Annex IV of EU regulation 1223/2009). In other regions that specify limits for particular heavy metals and their compounds, these limits vary quite widely. For arsenic, the acceptable level is 2 ppm in the United States and 3 ppm in China, but only 0.5 ppm in Germany according to the BVL's technically unavoidable limit. Similarly, the limit for lead contamination specified in United States and China (10 ppm) is five times the German value. Given these discrepancies, it is difficult to understand how we can guarantee consumer safety without a straightforward scientifically based evaluation of safe exposure levels. If safe limits were set according to the toxicological evidence, which should be regarded as a single global knowledge resource, then we should expect to see consistency in definitions and specifications between different regulatory authorities.

The current level of non-harmonisation in this regard may arouse suspicions among consumers and tend to make them dubious about the safety of cosmetic products. A more systematic approach to defining these limits would likely help to reassure end users as well as minimising adverse health outcomes. However, most of the safety assessment reports on the market do not address the calculation of allowable heavy metal levels as Responsible Persons (i.e., having ultimate responsibility for the products' safety), often meaning that they are unclear on the technically unavoidable limits of impurities and how safe these products will be.

Another general weakness of many current regulations is that they contain no clear definition of an 'unavoidable' level of impurities, as is the case for the German BVL. This attempt to define technically unavoidable limits is important, but the published values were derived from a seemingly arbitrary cutoff point (90th percentile) among heavy metal concentrations sampled over a range of representative products. Although this seems like a reasonable means of identifying the levels of contamination that are achievable with best manufacturing practice, the goal of setting permissible levels of heavy metals in cosmetic products should be based on improving their safety. The process should therefore consider the toxicological profiles of the relevant substances, rather than relying on technical considerations alone. If current practices do not permit contaminant levels consistently below safe concentrations as indicated by the toxicological evidence, the need for new manufacturing technologies to improve consumer safety could thus be identified. In addition to a more systematic approach to defining safe limits as outlined above, such measures would bring much-needed transparency to the industry and would also likely improve consumer confidence.

There are also issues with monitoring of product safety and legal compliance. For example, whereas testing of heavy metals in cosmetic products is mandatory in China, it relies on random spot checks in Europe. End users in the EU therefore have no reassurance that any given cosmetic product is within safe limits for heavy metal content, whereas consumers in the Chinese market will know that the product they are using has been tested. It seems advisable that this aspect of product safety should also be harmonised.

4. Conclusion

In general, heavy metal contamination in cosmetic products should be avoided due to their hazardous nature. However, it is clear that contamination with these substances cannot be avoided completely, and they are sometimes constituents of useful ingredients, thereby implying the need to establish acceptable safe limits. Regulatory compliance, and more importantly consumer safety, then rely on whether the content of various heavy metals is within the proposed limits set by the relevant regulatory bodies. The lack of harmonisation between these standards, and the inconsistencies between limits for different heavy metals across different jurisdictions, might lead to confusion for authorities and manufacturers alike. At present, there is no clearly defined international standard that all actors involved in bringing these products to market can follow.

We propose such a standard, based on clear toxicological evidence for each heavy metal of concern, to provide clarity for both manufacturers and regulators, as well as transparency over product safety for consumers. In defining technically unavoidable levels of contamination, which is an important regulatory role, clarity must be given regarding both evidence-based safe limits to avoid adverse health outcomes, and the best manufacturing processes to achieve these limits. We encourage ongoing conversations between regulatory authorities and industry groups, at an international level, to establish clearly defined global standards for heavy metal contamination limits and best practices to adhere to them, and to identify suitable pathways to enable industry-wide implementation of these guidelines.

References

Bhattacharjee, P. C. D. (2013). Systems biology approaches to evaluate arsenic toxicity and carcinogenicity: an overview. *International Journal of Hygiene and Environmental Health*, 574–586.

Bocca, B., Forte, G., Petrucci, F., & Cristaudo, A. (2007). Levels of nickel and other potentially allergenic metals in Ni-tested commercial body creams. *Journal of Pharmaceutical and Biomedical Analysis*, 1197–1202.

BVL (2017). Technically avoidable heavy metal contents in cosmetics. *Journal of Consumer Protection and Food Safety*, 12:51–53.

Dorne, J.-L., Kass, G., Bordajandi, L., Amzal, B., Bertelsen, U., Castoldi, A., … Verger, P. (2011). Human risk assessment of heavy metals: principles and applications. *Met Ions Life Sciences, 8*, 27–60.

Edward, M. J. (2000). Metals and the skin: Topical effects and systemic absorption by R. H. Guy, J. J. Hostynek, R. S. Hinz, and C. R. Lorence. *Journal of Toxicology: Cutaneous and Ocular Toxicology*, 165–166.

Gibb, H., Haver, C., Gaylor, D., Ramasamy, S., S. Lee, J., Lobdell, D., … Sams, R. (2011). Utility of recent studies to assess the National Research Council 2001 estimates of cancer risk from ingested arsenic. *Environmental Health Perspectives*.

Guy, R., Hostýnek, J., Hinz, R., & Lorence, C. (1999). *Metals and the skin: Topical effects and systemic absorption.* Boca Raton, FL: CRC Press.

Health Canada. (2006). *Guidelines for Canadian drinking water quality: Guideline technical document – arsenic.*

Hostynek, J. (2001). Lead, manganese and mercury: Metals in personal-care products. *Cosmetics and Toiletries Magazine*.

Järup, L. (2003). Hazards of heavy metal contamination. *British Medical Bulletin, 68*, 167–182.

Karri, V., Schuhmacher, M., & Kumar, V. (2016). Heavy metals (Pb, Cd, As and MeHg) as risk factors for cognitive dysfunction: A general review of metal mixture mechanism in brain. *Environmental Toxicology and Pharmacology*, 203–213.

Mahurpawar, M. (2015). Effects of heavy metals on human health. *International Journal of Research*, *530*, 1–7.

MILESTONE. (2021). *White paper: ISO 21392: A turning point in heavy metals analysis of cosmetic products.*

Natural Health Products Directorate. (2007, June). *Evidence for quality of finished natural health products*.

Patrick, L. (2006). Lead toxicity, a review of the literature. Part 1: Exposure, evaluation, and treatment. *Alternative Medicine Review: a Journal of Clinical Therapeutic*, *11*(1), 2–22.

Rebelo, F. M. C. E. (2016). Arsenic, lead, mercury and cadmium: Toxicity, levels in breast milk and the risks for breastfed infants. *Environmental Research*, 671–688.

Sprinkle, R. (1995). Leaded eye cosmetics: a cultural cause of elevated lead levels in children. *The Journal of Family Practice*, 358–362.

Tamara, T., & Attard, E. (2022). Heavy metals in cosmetics. *Environmental impact and remediation of heavy metals*.

USHHS, & USCFSAN. (2016). *Lead in cosmetic lip products and externally applied cosmetics: Recommended maximum level guidance for industry: Draft guidance.*

Hepp, N. et al (2014). Survey of Cosmetics for Arsenic, Cadmium, Chromium, Cobalt, Lead, Mercury, and Nickel Content the *Journal of Cosmetic Science* (May-June;65(3):125-45.