Universidade de Lisboa

Faculdade de Farmácia

Risk Assessment of Heavy Metals in Lipsticks

Dany de Figueiredo

Mestrado Integrado em Ciências Farmacêuticas

2019

Universidade de Lisboa

Faculdade de Farmácia

Risk Assessment of Heavy Metals in Lipsticks

Dany de Figueiredo

Monografia de Mestrado Integrado em Ciências Farmacêuticas apresentada à Universidade de Lisboa através da Faculdade de Farmácia

Orientador: Doutor Arturo Hardisson de la Torre, Professor catedrático

Co-Orientador: Doutor Rui Loureiro, Professor associado

2019

Resumo

Cosméticos faciais, tais como os batons, são um dos itens mais usados no mundo. Estes produtos são aplicados diretamente na pele, podendo causar exposição local a alguns ingredientes que podem pôr em risco a saúde, pela presença de metais pesados. Estes podem ser intencionalmente adicionados à sua composição ou estar presente em concentrações ínfimas na forma de impurezas. Apesar das concentrações de metais pesados serem objeto de estudo em numerosos artigos, a clarificação de como os níveis obtidos se relacionam com possíveis efeitos adversos para a saúde humana é exigente. Neste estudo, a concentração de metais pesados presentes em 45 amostras de batons provenientes da China e da Europa foi determinada, usando a Espetrometria de Emissão Ótica com Plasma Acoplado Indutivamente (ICP-OES) como método analítico, para no fim se proceder à avaliação de risco. Além disso, efetuaram-se análises estatísticas, estudos de correlação, cumprimento da regulação internacional e avaliação da ingestão. A concentração de metais nas amostras apresentou uma grande variação, o que pode ser atribuído à qualidade das matérias primas empregues na sua produção. Também encontrámos diferenças estatísticas significativas entre as concentrações de Ba, Cd, Cu e Li e correlações positivas entre B/Cd, Ni/Cd, Cd/Fe e K/Pb. A maioria das amostras cumpre a legislação aplicável. Apesar da falta de informação para uma completa análise de risco, detetou-se uma MoS abaixo de 100, proveniente da exposição oral aos batons, tanto da China como da Europa, pelo que os riscos na sua utilização não devem ser menosprezados. Na avaliação da ingestão, obteve-se um valor de contribuição de 3,39% da quantidade diária tolerável do Pb para crianças, o que também é motivo de inquietação, se considerarmos as restantes fontes de exposição. Com tudo isto, podemos concluir que os produtos cosméticos constituem uma importante via de exposição crónica a estas substâncias e, portanto, possíveis efeitos adversos. Para minimizar os possíveis riscos inerentes à utilização de cosméticos, uma cooperação mais forte e constante que envolva especialistas em toxicologia é recomendada, para avaliar a segurança dos batons, inclusive os ingredientes utilizados nos mesmos.

Palavras-chave: Análise; impurezas; risco; metais pesados; batons

Abstract

Facial cosmetics, such as lipsticks, are used around the world by millions of consumers. These products are applied directly to the skin and may cause local exposure to certain ingredients that could be dangerous to health, like heavy metals, which may be part of the composition or in trace concentrations as impurities. Even though the concentrations of heavy metals have been studied in numerous articles, the clarification of how the described levels relate to possible adverse health risks is demanding. In this study, the concentration of heavy metal in 45 samples of lipsticks from China and Europe was determined using Inductively Coupled Plasma Optical Emission Spectrometry (ICP-OES) as an analytical technique, ultimately to evaluate the risk to human health. Furthermore, statistical analysis, correlation studies, compliance with international regulation and intake assessments were also performed. The metal concentrations in the lipsticks presented a large variation, which may be attributed to the quality of the raw materials used in its production. We also found statistically significant differences between the concentrations of Ba, Cd, Cu and Li and positive correlations between B/Cd, Ni/Cd, Cd/Fe, and K/Pb. In addition, most of the samples fulfill the international regulation regarding toxic elements limits. Although critical data was missing to conduct the risk assessment, we detected an MoS from oral exposure to Pb in lipsticks from China and Europe both below the safety margin of 100, so the possible health risks due to the presence of this metal in lipsticks should not be underestimated. Another concerning result was the 3,39% contribution to the daily intake found for Pb in the children intake assessment conducted. With all this, it could be concluded that cosmetic products can constitute an important route of chronic exposure to these substances and, therefore, constitute a concern to health. To minimize any possible risk cosmetics may pose to human health, tighter cooperation involving toxicology specialists is recommended, in order to assess the safety of lipsticks and their wide share of ingredients on a constant basis.

Keywords: Assessment; impurities; health risk; heavy metals; lipsticks.

Acknowledgments

In order to write a proper acknowledgment, one has to think of all the options, actions, persons and moments that took us here, which is easier said than done. Even so, I will make an effort to write something that's exactly the opposite of this Master Thesis, also known as an "all facts and no flavor" work.

Being, among other things, a methodical, exacting and…patient student – How can we endure 5 years of a Master's Degree, without being patient? Short answer: we could not. Afterward, what are 5 years? They are just 5 turns around the sun, if you think about it – I have, in this moment of reflection, to thank all my colleagues, some of them also my friends, that helped me in this quest, either in group works, laboratory, practical or theoretical classes, finals preparation…basically, everything that comes with the Pharmaceutical Sciences course (and not curse!). Maybe because they fulfill my flaws, maybe because we complemented each other's flaws, the fact is, we did it! As someone once said, "Alone we go faster, but together we go further".

Unfortunately, I cannot thank individually to all my colleagues, not only because we were more than 215 when we started this journey, but also because each filter I try to apply to give me an output I can work with, ends up in a huge number of names, which is normal, because if we think in the curricular units we shared – 48; in the works we presented – more than 50; in the exams we were submitted to – about 97, according to my calculus and including theoretical, practical and laboratory exams. This being said, there are 9 names I must mention – and please, to those not here included, pardon me – José Pio, Ariana Colaço, Bruno Peniche, Mariana Cunha, Filipe Rodrigues, Letícia Carraro, Francisco Lopes, Beatriz da Branca, and Henrique Roberto. I don't know if as we age, we tend to become more sentimental, but the fact is, without you, things would not be the same, and for that, I give you my utmost respect and gratitude.

Another thrilling event in this long campaign was the Erasmus. I had my doubts about doing it, getting outside of my comfort zone, going away to another country, but all things considered, if we were meant to stay in one place, we'd have roots, instead of feet. Although this is not the moment to speak about how this exchange program was useful for me, it is, however, the moment to thank all the amazing people I met along the way, especially Sara Lara Torres, to whom I have to give credit for much of the work depicted in this Thesis, Arturo Hardisson, Angel Gutiérrez, and Soraya Paz.

Finally, the family is something we constantly take for granted, and saving them for last may very well reflect once more that way of thinking. But not on my watch. To my family and, although not all of them, at least most of my relatives, I have to thank for the patience, tolerance, and understanding they too had towards me, while I was unavailable during business days, weekends, holidays, birthdays and vacations. To them, please remember that “Good times don’t last forever, but neither do the bad”.

And because everything in life is temporary, I must thank those who are not among us anymore. Those I can only remember. Those I expect to see once again. From those, one is very special, and it doesn’t come easy for me to remember. Nor it should. As Jay Neugeboren once said, “A wife who loses a husband is called a widow. A husband who loses a wife is called a widower. A child who loses his parents is called an orphan. There is no word for a parent who loses a child. That’s how awful the loss is.”. This being said, I can only thank my parents for teaching me what resilience looks like, day after day, and hope my sister keeps praying for us. We too continue to do, as faith is believing and trusting in something one cannot see.

Since there comes a time when we have to face the things we fear the most – the Thesis, once again, and because “Last words are for fools who haven’t said enough.” as the German philosopher Karl Marx shouted, let’s proceed with our work.

Table of Contents

List of Figures

List of Tables

List of Abbreviations and Acronyms

^{0}C: Degrees Celsius

ADI: Admissible Daily Intake

BMD: Benchmark dose

BW: Bodyweight

CDC: Centers for Disease Control and Prevention

EFSA: European Food Safety Authority

EPA: United States Environmental Protection Agency

EU: European Union

FDA: Food and Drug Administration

HERAG: Health Risk Assessment Guidance for Metals

HI: Hazard Index

HQ: Hazard Quotient

IARC: International Agency for Research on Cancer

ICP-OES: Inductively Coupled Plasma Optical Emission Spectrometry

LL: Long Lasting

LOAEL: Lowest Observed Adverse Effect Level

LOD: Limit of Detection

Lot.: Batch number

ME: Metallic Effect

MoS: Margin of Safety

NA: Not Available

NOAEL: No Observed Adverse Effect Level

POD: Point of Departure

Ppm: Part per million, equivalent to mg kg^{-1}

RDI: Recommended Daily Intake

RfD: Reference dose

SCCS: Scientific Committee on Consumer Safety

SD: Standard Deviation

TDI: Tolerable Daily Intake

TWI: Tolerable Weekly Intake

UL: Upper-Level Intake

US: United States

Metals

Al: Aluminum

B: Boron

Ba: Barium

Ca: Calcium

Cd: Cadmium

Co: Cobalt

Cr: Chromium

Cu: Copper

Fe: Iron

K: Potassium

Li: Lithium

Mb: Molybdenum

Mg: Magnesium

Mn: Manganese

Na: Sodium

Ni: Nickel

Pb: Lead

Sr: Strontium

V: Vanadium

Zn: Zinc

1. Introduction

Cosmetics intended to give color to the lips have been used since the Sumerians, back in 7000 B.C. Although they started with a reddish color and consisted of bees-wax, tallow, and pigment, the custom has been passed down through generations, starting with the Egyptians to present-day civilizations, where the lipstick, with the push-up holder style, introduced around 1920, still remains the favorite product among all lipstick formulas yet invented (1).

Even though the story of cosmetics has started in ancient times, it was in the past few years that their use increased worldwide, due to both the quest for individual beautification and the enhanced pressure of marketing and product advertisement (2,3).

Nowadays, lipsticks evolve to a variety of different ingredients, like numerous waxes, oils, polishes, antioxidants, emollients, dyes pigments as well as filling material such as mica, silica, fish scales, titanium dioxide to obtain different colors, properties, and aspects (4). However, the consumer concerns about toxic element contents of this, and other types of cosmetics has also seen remarkable growth, as various articles point out (3–6). In fact, cosmetic products are a possible source of daily, population-wide and frequently long-term exposure to a variety of chemicals (6). As stated by Health Canada, 100% of all cosmetics products have a positive result when tested for Ni. Over 90% tested positive for Pb, and, on average, incorporate 4 out of 8 metals of concern, which are As, Be, Cd, Pb, Hg, Ni, Se and Ti (3). Therefore, the use of cosmetics cannot be excluded as a possible, although less obvious, source of exposure to naturally occurring metals (7).

In general, heavy metals are those whose density is five times greater than the density of water (8) and even if some trace metals are essential for human health, like Fe, Cu, and Zn, when present in high concentration, they become toxic (9). Indeed, the metal content in cosmetic products across several regions of the planet has been studied in recent articles (3–6,9–22), with Pb, Cd, and Cr being detected in several lipstick samples (23).

But, how do heavy metals end up in lipsticks? In fact, these can be explained by two main reasons: either heavy metals can be in ingredients that naturally contain them, since the components of cosmetic products often include a compound of different metals (18,19) or, are polluted with them during the production step or by the containers they are stored in, and, consequently, be present as impurities (20). Some of the metals that can be part of the pigments used to achieve a vast variety of colors are Chromium, Cobalt, Copper, Nickel, Cadmium, and Lead (ordered according to their atomic number)(19).

To give a better understanding, if we focus on Pb, for example, it is known to be an environmental contaminant, that occurs both naturally, in the earth's crust, and derived from several human activities, in organic and inorganic forms (6). If we consider that it has been extensively used in consumer products, gasoline, and manufacturing processes, it's not a surprise that it's widely distributed thought-out the environment (24), neither the fact that it is present in the manufacture of raw materials, dyes, and pigments used in the cosmetic industry (21).

Pb, alongside Cd and Al, are toxic metals known to be stable, with a long biological half-life, non-biodegradable, lacking a biological function, and being accumulative in the human organism (25), therefore, capable of several types of toxic effects (17,26). Cd and Pb, for instance, participate in enzymatic reactions that are Zn-dependent and can lead to renal dysfunction, endocrine disruption, and hypertension (9). Al has been associated with neurotoxicity in dialysis patients treated with aluminum-containing dialysis fluids and aluminosis, in the case of high dust exposure workplaces. There are, as well, studies showing a higher risk for Alzheimer's disease in individuals with chronic aluminum exposure and others trying to figure out if there is a link between aluminum and breast cancer (27). Ni compounds, on the other hand, are considered carcinogens group 1, by the International Agency for Cancer Research (IARC) (25), as well as Cd and its compounds, and Cr (VI), both associated with lung cancer, while Cr (VI) has also been linked to stomach tumors (22). Nonetheless, it's important to not include Cr and Ni in the toxic metals category, since they are both essential micronutrients, hence with biological functions (28,29). Finally, Pb has been categorized by IARC, in group 2B of carcinogens (30,31), and its harmful effects are well documented. Since it bioaccumulates in various organs such as brain, kidney, heart, digestive system, and bone (26), it is capable of both acute and chronic poisoning (2), and has a variety of symptoms, which include vomiting, convulsions, adverse effects on central nervous system cells, sometimes leading to permanent brain damage or even death, anemia, as well as pathological changes of various organs (4,24). Most of these symptoms are present in saturnism, an ancient name for lead poisoning (32). In terms of lead body burden, more than 90% is localized in bone, having an average half-life of more than 20 years. Bone releases lead, during increased bone turnover periods in women's lives, such as menopause, pregnancy, and lactation and since lead can cross the placenta, it has been linked with premature delivery, low birth weight and intrauterine fetal death (24). Besides that, exposure to lead is the strongest contaminant in the environment that interferes with healthy reproductive function in adult females (3).

In accordance with the European Regulation No. 1223/2009, there are substances (listed in Annex II) that are prohibited in cosmetic products, which includes all the compounds of Cd, Cr, Pb, among other metals, in the case of lipsticks (33). Nevertheless, due to their persistent and widespread nature, the presence of trace amounts of metallic elements in cosmetic products is practically inevitable, even when they are manufactured under good manufacturing practices (34), and consumers have no way to perceiving their own risk, since cosmetics companies are not required to report on this kind of impurities (21).

Considering all these findings, and since cosmetic consumers expose themselves to heavy metals in small amounts, but for a prolonged period of time, which may be significant in terms of developing chronic health risk, defined as an irreversible response characterized by a gradual onset of long duration, following a constant or continuous exposure period to a low toxicant dose (13), we found useful to determine the levels of 20 metals (Li, B, Na, Mg, Al, K, Ca, V, Cr, Mn, Fe, Co, Ni, Cu, Zn, Sr, Mo, Cd, Ba and Pb) in lipsticks, in order to realize if they are within acceptable limits, with emphases on the toxic metals here included (Al, Cd, and Pb), for which we will perform a human health risk assessment.

After searching the literature, no studies were found that assemble the concentration of these 20 metals in lipsticks, with Cd and Pb being the mainly determined metals, which makes sense, since they are both highly toxic metals, and, although in a lesser degree, Cr, Mn, Fe, Co, Ni, Cu, and Zn (10,19,35).

The use of lipstick has been reported to be not only a risk factor but also an environmental trigger for developing systemic lupus erythematosus (3), which is an autoimmune disease of yet undetermined cause (36) and, although the skin serves as a protective barrier, some ingredients and contaminant penetrate the face, lips, or eyes and are able to produce adverse effects, both local or systemic (23). There are multiple exposure scenarios related to cosmetics, with dermal exposure being considered the most important route for cosmetics products since most of them are applied topically. However, oral exposure can also occur, especially if used in and around the mouth as well as from hand-to-mouth contact. Inhalation exposure is typically regarded as insignificant (12). If we think in lipsticks, that are applied to mucous membranes, then the danger shall be even greater. In addition to these, lip products also have a higher risk of direct oral ingestion (37), therefore aggravating the toxic effects of its ingredients (2).

Cosmetic's matrix is a challenge regarding metal analysis because it is constituted by many ingredients including oils, waxes, dyes, and pigments, which may include refractory minerals as alumina, silica, mica, and titanium dioxide (21). Determining lead, when present at very low concentrations, for instance, is frequently difficult, because of insufficient sensitivity of the method as well as the matrix interferences (15). Therefore, we intend to use a highly sensitive method for the determination of metals, called inductively coupled plasma optical emission spectrometry (ICP-OES) (38).

2. Objectives

Our primary objective is to determine the concentration of 20 metals in lipsticks. Secondly, we want to evaluate if there is a statistically significant difference between lipsticks of distinct origins - China and Europe - regarding their metal content. In addition, investigate the correlation between toxic metals and the other micro and macro elements in the samples. In fourth place, verify if the levels of metals are within acceptable limits, using international guidelines as a reference. Fifthly, a non-cancer and cancer risk assessment for the toxic metals is discussed. Finally, execute an intake assessment, using different scenarios.

3. Materials and Methods

3.1. Literature Search

In February 2019, we conducted a literature review using PubMed in order to identify articles on metals in lipsticks, that were published during or after the year 2005. Keywords included “heavy metals”, “trace metals”, “toxic metals”, “metals”, “lipsticks”, “cosmetics”, “ICP-OES”, “risk assessment” and “assessment”.

3.2. Samples

This study used 45 samples of lipsticks from different brands, colors, and origins, obtained from supermarkets and traditional markets across Tenerife (Canary Islands, Spain) between February and April 2019. They were divided into two sample groups, which represented two different origins, China, listed in Table 1, and Europe, listed in Table 2. Samples were stored at room temperature until analyses.

Table 1. Lipstick samples from China

Nº	*Type of sample/Brand/Lot.*	*Origin*	*Wet sample weight (g)*
1	Purple/Brand 1/0196-016	China	2,815
2	Red/Brand 1/0196-010	China	3,551
3	Red/Brand 2/180121	China	3,854
4	Brown/Brand 2/180121	China	3,833
5	Red/Brand 3/AK001469	China	3,314
6	Brown/Brand 3/AK001469	China	2,730
7	Dark Brown/Brand 3/AK001469	China	3,227
8	Purple/ Brand 3/AK001469	China	3,587
9	Black/Brand 4/AH12-001	China	3,683
10	Pink/Brand 4/A156-001	China	2,892
11	Red/Brand 4/A049-006	China	2,710
12	Purple/Brand 4/A150-001	China	3,317
13	Pink Magico/Brand 4/A173-001	China	3,254
14	Pink L.L/Brand 4/A179-001	China	3,362
15	Pink/Brand 5/F244	China	0,892
16	Pale Pink/Brand 5/F244	China	0,928
17	Brown/Brand 5/F244	China	0,941
18	Brown/Brand 6/NA	China	3,830
19	Brown LL/Brand 6/AH07-001	China	3,612
20	Purple LL/Brand 6/AH07-001	China	3,670
21	Blue ME /Brand 6/NA	China	4,119
22	Gold ME/Brand 6/NA	China	4,070

Looking at table 1, we can see that the manufacturing batch number, represented as Lot., is not available for samples 18, 21 and 22. It is worth mentioning that they are all from the same brand.

Table 2. Lipstick samples from Europe

Nº	*Type of sample/Brand/Lot.*	*Origin*	*Wet sample weight (g)*
23	Red/Brand 7/2270	Europe	3,626
24	Rose/Brand 8/1472104	Europe	3,971
25	Pink/Brand 8/0752104	Europe	4,051
26	Brown/Brand 8/0462104	Europe	4,069
27	Brown Glitter/Brand 9/C099	Europe	5,156
28	Pink/Brand 9/A257	Europe	4,392
29	Red/Brand 9/C191	Europe	4,243
30	Purple Glitter/Brand 9/C071	Europe	4,810
31	Purple Glint/Brand 10/0169	Europe	4,383
32	Light Pink Neon/Brand 10/2128	Europe	4,358
33	Dark Pink Neon/Brand 10/0289	Europe	4,046
34	Pink Matte/Brand 10/0189	Europe	4,596
35	Red Matte/Brand 10/0189	Europe	4,612
36	Purple/Brand 10/0239	Europe	4,240
37	Pink/Brand 10/0239	Europe	4,262
38	Red/Brand 10/0239	Europe	4,112
39	Light Brown/Brand 10/0239	Europe	4,198
40	Dark Brown/Brand 10/0239	Europe	4,219
41	Red Matte/Brand 11/0188	Europe	4,910
42	Pink Acid/Brand 11/1517	Europe	4,052
43	Orange Matte/Brand 11/0188	Europe	5,114
44	Pink Matte/Brand 11/0188	Europe	4,956
45	Orange Acid/Brand 11/1717	Europe	4,407

3.3. Instrumentation

- Precision balance (Metler-Toledo PB153-S, USA)
- Oven (P-Selecta, Spain)
- Hot plate (P-Selecta, Spain)
- Muffle furnace (Nabertherm P330, Germany)
- Inductively Coupled Plasma Optical Emission Spectrometer ICAP 6300 Duo Thermo Scientific (Waltham, MA, USA).

3.4. Sample Preparation and Analysis

The lipsticks were open and weighted in porcelain capsules, using a precision balance. The average weight of the samples was 3,75g. After this, the samples were dried in an oven at 80ºC, for at least 24h or until constant weight. Digestion process was then initiated, adding 65% HNO_3 to the samples, in order to reduce interferences due to the organic matter and also to facilitate the extraction of the metals (14). A hot plate at 100 ± 20ºC inside a fume hood chamber was used to accelerate the process, until complete evaporation of the nitric acid. Concluded this step, the samples were incinerated using a muffle furnace, with a 12h period to reach 450ºC, and maintained that temperature for 24 hours. White and/or colored ashes should be obtained since it depends on the pigments used in each lipstick. If we obtained black ashes, we needed to repeat the digestion with 65% HNO_3 and incinerate again for 12h at 450ºC. One aspect to take into consideration is that the muffle furnace must be programmed to a maximum temperature of 450ºC since above this temperature there are metallic losses due to volatilization or retention (39). At last, the ashes were dissolved with 1,5% HNO_3, so the heavy metals do not precipitate, to a volume of 25 mL, and stored in disposable plastic containers at room temperature, until further analysis. The metals were determined by inductively coupled plasma optical emission spectrometry (ICP-OES), which is a highly sensitive method used for the determination of metals and offers an outstanding reproducibility rate (38). The sample preparation and analysis process are resumed in Figure 1. This method was performed according to the laboratory's internal procedures.

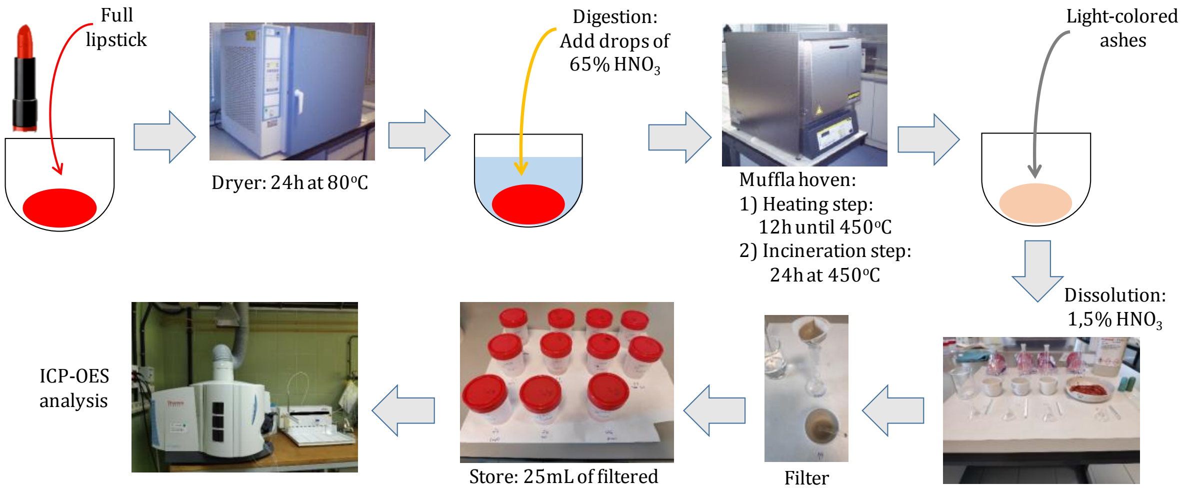

Figure 1. Sample treatment and analysis

The equipment introduces an Argon (Ar) flow in a radio frequency field which reaches high temperatures, up to 10000 ºC, necessary to cause the ionization, excitation, and emission of radiation by the elements incorporated in the analyzed sample. The measurement of the radiation emitted by the atoms and ions is, consequently, what is determined by the ICP-OES, expressed in mg L^{-1}. The detection and quantification limits of the ICP-OES apparatus are represented in Table 3, so as the wavelengths (nm) for each analyzed metal and the instrumental conditions.

Table 3. Detection and quantification limits of ICP-OES, wavelengths for each metal and instrumental conditions

Metal	*Wavelength (nm)*	*Detection limit (mg/l)*	*Quantification limit (mg/l)*
Al	167,0	0,004	0,012
B	249,7	0,003	0,012
Ba	455,4	0,001	0,005
Ca	317,9	0,58	1,955
Cd	226,5	0,0003	0,001
Co	228,6	0,0006	0,002
Cr	267,7	0,003	0,008
Cu	327,3	0,004	0,012
Fe	259,9	0,003	0,009
K	769,9	0,565	1,884
Li	670,8	0,005	0,013
Mg	279,1	0,583	1,943
Mn	257,6	0,002	0,008
Mo	202,0	0,0007	0,002
Na	589,6	1,097	3,655
Ni	231,6	0,0007	0,003
Pb	220,3	0,0003	0,001
Sr	407,7	0,0007	0,003
V	310,2	0,001	0,005
Zn	206,2	0,002	0,007

Model: iCAP 6300 Duo de Thermo Scientific
Gas flow: 0,5 L/min
Approximate RT power: 1150 W
Setting time: 0 s
Injecting the sample to flow pump: 50 rpm (stabilization flow, analysis flow)

3.5. Statistical Analysis

Statistical analysis were executed with IBM SPSS Inc., version 23.0. Initially, a normality study was performed, in order to analyse the distribution of data, using Kolmogorov-Smirnov and Shapiro-Wilk tests. To evaluate the homogeneity of variances, Levene statistics tests were also performed. The results did not follow a normal distribution, so the conditions for a parametric test were not met. Instead, a no parametric test for independent samples was conducted, the Mann-Whitney U test, in order to find the possible differences between the two origins of lipsticks. P-values $\leq$ 0,05 were considered statistically significant. For the statistical study, the data was treated based on lipsticks origin. Correlation tests were also conducted, using Spearman's rank correlation coefficient.

3.6. Human Health Risk Assessment

Two exposure pathways for heavy metals from lipsticks have been determined - oral and dermal routes. Taking into account these two routes, it has been decided to use the risk assessment models offered by the SCCS (40) and US EPA (41), to calculate the hazard associated with the presence of heavy metals in this type of cosmetics.

3.6.1. The Scientific Committee of Consumer Safety (SCCS) model

The safety evaluation of heavy metals in cosmetics has been calculated with Eq. (1) Margin of Safety (MoS), as it is explained in the SCCS Notes of Guidance (40), where RfD ($mg \cdot kg^{-1} \cdot day^{-1}$) is a reference dose of heavy metals and SED ($mg \cdot kg^{-1} \cdot day^{-1}$) is the Systemic Exposure Dose. An MoS≥100 indicates that the cosmetic ingredients submitted for evaluation are safe for human health.

$$MOS = \frac{POD}{SED} \tag{1}$$

The POD used was based on the NOAEL of each toxic metal, which were 125 $mg \cdot kg^{-1} \cdot day^{-1}$ for Al (42); 0,019 $mg \cdot kg^{-1} \cdot day^{-1}$ for Cd (43) and 0,00286 $mg \cdot kg^{-1} \cdot day^{-1}$ for Pb (44). The parameter SED could be referring to either oral dose or dermal dose.

The SED_{dermal} ($mg \cdot kg^{-1} \cdot day^{-1}$) is calculated according to Eq (2), where EX (%) is the amount of metal a person is exposed to when using lipstick, referred to the average weight of the samples, and DA (%) is the percentage of absorption of metals throughout the skin. In the absence of data and, because the log K_{ow} of the three metals is between -1 and 4 (45) and their melting point is greater than 200ºC, a DA of 10% can be estimated for each one (46). An *a posteriori* safety evaluation about metals in cosmetics used 0,8% and 0,3% for the dermal absorption of Cd and Pb, respectively (7), and so did we. Sadly, Al was not evaluated in the previous article. However, a study of ^{26}Al chlorohydrate absorption, one of the most used antiperspirant components, concluded an average dermal absorption of 0,028% (47), and this was the value we worked with.

$$SED_{dermal} = EX/100 \times DA/100 \tag{2}$$

Meanwhile, the SED_{oral} ($mg \cdot kg^{-1} \cdot day^{-1}$) is determined with Eq. (3), where OA (%) is the percentage of absorption of metals throughout ingestion. The OA for Al, Cd and Pb are 0,1% (48), 5% (49) and 60% (50), respectively.

$$SED_{oral} = EX/100 \times OA/100 \quad (3)$$

In both equations, (2) and (3), the parameter EX ($mg \cdot kg^{-1} \cdot day^{-1}$) is the same and can be calculated with the Eq. (4), where C ($mg \cdot g^{-1}$) is the concentration of heavy metal in lipstick, q (0,9 $mg \cdot kg\ b.w.^{-1} \cdot day^{-1}$) is the relative daily amount applied of lipstick, and F_{ret} (1,0) is a unitless factor retention (40).

$$EX = C \times q \times F_{ret} \quad (4)$$

3.6.2. The Environmental Protection Agency of the United States (US EPA) model

The US EPA health risk assessment includes carcinogenic and non-carcinogenic guides (41). The Eq. (5) determines the Chronic Daily Intake ($mg \cdot kg^{-1} \cdot day^{-1}$) for dermal exposure ($CDI_{dermal}$), where C ($mg \cdot kg^{-1}$) is the concentration of heavy metal in lipstick, SA is the exposed skin area (4,8 cm^2) (40). AF is the adherence factor (0,1 $mg \cdot cm^{-2}$), ABS is a unitless dermal absorption factor (0,1), EF is the exposure frequency (350 $days \cdot year^{-1}$), ED is the exposure duration (30 years), BW is the body weight (70 kg) and AT is the averaging time (25550 days).

$$CDI_{dermal} = \frac{C \times SA \times AF \times ABS \times EF \times ED \times 0{,}001}{BW \times AT} \quad (5)$$

The Chronic Daily Intake ($mg \cdot kg^{-1} \cdot day^{-1}$) for oral absorption ($CDI_{oral}$) is defined as set forth in Eq. (6) being C ($mg \cdot kg^{-1}$) the concentration of heavy metal in lipstick, EX the amount of lipstick applied per day (0,087 $mg \cdot day^{-1}$) (51), FI a unitless fraction ingestion (1), EF the exposure frequency (350 $days \cdot yea^{-1}$), ED the exposure duration (30 years), BW the body weight (70 kg) and AT the averaging time (25550 days).

$$CDI_{oral} = \frac{C \times EX \times FI \times EF \times ED \times 0{,}001}{BW \times AT} \quad (6)$$

Once the CDIs are calculated, the carcinogenic and non-carcinogenic risk is evaluated for each exposure pathway. Firstly, Eq. (7) is used for calculating the carcinogenic risk from individual heavy metals, where SF is the slope factor of a dangerous substance. The oral SF of Cd and Pb are 15 and 0,0085 ($mg \cdot kg^{-1} \cdot day^{-1}$), respectively (30,52). The SF for Al could not be found.

$$Cancer\ risk = CDI \times SF \quad (7)$$

The total carcinogenic risk is calculated with the Eq. (8). The values have to be less than or equal to 10^{-4} to consider that there is no risk (41).

$$Total\ cancer\ risk\ oral = \sum_{k}^{n} CDI_{k} \times SF_{k} \tag{8}$$

When the CDI from oral and dermal exposure has been calculated, the non-carcinogenic risk is determined with a Hazard Quotient (HQ) with the Eq. (9). for both exposure pathways. The RfD values for Al, Cd, and Pb are 0,0004 mg kg b.w.$^{-1}$ day^{-1}; 0,0005 mg kg b.w.$^{-1}$ day^{-1} (23) and 0,00063 mg kg b.w.$^{-1}$ day^{-1}, respectively. An HQ≤1 indicates that the cosmetic ingredients submitted for evaluation are safe for human health.

$$HQ = \frac{CDI}{RfD} \tag{9}$$

The total non-carcinogenic risk is calculated with the Eq. (10), which refers to a Hazard Index (HI) that estimates the risk of mix heavy metals contaminants, where the values have to be less than or equal to 1 to consider that there is no risk (41).

$$HI = \sum_{k}^{n} HQ_{k} \tag{10}$$

4. Results and Discussion

4.1. Concentration of 20 metals in the lipstick samples

In the samples submitted to analysis, it was determined a total of 4 macroelements: Na, K, Ca and Mg; 13 microelements: B, Ba, Co, Cr, Cu, Fe, Mn, Mb, Li, Ni, Sr, V and Zn; and 3 toxic metals: Al, Cd, and Pb (38). The results of the average concentration, minimum and maximum value of these 20 metals in the lipstick samples, based on their origin, either China or Europe are expressed in Table 4. The individual metal value for each of the lipsticks analyzed can be seen in Table 5, in the case of toxic metals, and in point 7.1. and 7.2. of the Attachments, in the case of macro and microelements. For statistical analysis purposes, values below the LOD were considered as 0.

Table 4. Average concentration, minimum and maximum value of metals in the lipstick samples

	Al (mg/kg)	*B (mg/kg)*	*Ba (mg/kg)*	*Ca (mg/kg)*	*Cd (mg/kg)*
China					
Average ± SD	70,5 ± 61,8	2,6 ± 3,6	5,01 ± 5,01	737 ± 744	0,07 ± 0,08
Min. – Max.	2,0 - 291	0 – 11,30	0 – 20,4	29,5 - 2364	0 – 0,24
Europe					
Average ± SD	50,6 ± 19,6	1,14 ± 0,98	2,52 ± 4,3	302 ± 404	0,012 ± 0,01
Min. – Max.	3,5 – 74,5	0 – 4,3	0 – 21,4	0 - 1538	0 – 0,09
	Co (mg/kg)	***Cr (mg/kg)***	***Cu (mg/kg)***	***Fe (mg/kg)***	***K (mg/kg)***
China					
Average ± SD	0,09 ± 0,1	0,19 ± 0,37	5,78 ± 16,1	152 ± 227	113 ± 204
Min. – Max.	0 – 0,37	0 – 1,73	0,31 – 72,2	0 - 640	0 - 854
Europe					
Average ± SD	0,03 ± 0,03	0,08 ± 0,08	0,54 ± 0,14	92,4 ± 79,7	81 ± 99,1
Min. – Max.	0 – 0,24	0 – 0,28	0,25 – 0,93	7,1 - 598	0 - 441
	Li (mg/kg)	***Mg(mg/kg)***	***Mn(mg/kg)***	***Mo(mg/kg)***	***Na (mg/kg)***
China					
Average ± SD	0,71 ± 1,23	32,3 ± 37,2	5,57 ± 8,57	6,88 ± 21,4	715 ± 887
Min. – Max.	0 – 5,04	0 - 134	0,12 – 28,9	0 – 93,3	57,9 - 2820
Europe					
Average ± SD	1,05 ± 1,08	48,3 ± 57,7	2,64 ± 3,61	0,155 ± 0,4	480 ± 782
Min. – Max.	0 – 3,2	0 - 154	0,1 – 11,5	0 – 1,32	0 - 3228
	Ni (mg/kg)	***Pb (mg/kg)***	***Sr (mg/kg)***	***V (mg/kg)***	***Zn (mg/kg)***
China					
Average ± SD	0,12 ± 0,09	0,27 ± 0,38	3,06 ± 3,29	1,89 ± 7,93	14,8 ± 51,3
Min. – Max.	0,03 – 0,32	0,00 – 1,46	0,21 – 11,5	0, – 37,4	0,32 - 242
Europe					
Average ± SD	0,09 ± 0,08	0,42 ± 0,82	1,65 ± 1,97	0,41 ± 0,33	13,6 ± 33,5
Min. – Max.	0,03 – 0,41	0 – 3,39	0,23 – 8,42	0 – 2,34	0,2 - 141

NOTE: mg/kg of wet weight

Looking at the results, we can conclude that the macroelements with the highest concentrations are Ca and Na in both China and Europe samples. In the microelements, Fe was the metal with the highest value in both samples' groups. At last, in terms of toxic metals, Al was, by far, the dominant element. The metal concentrations in the lipsticks have a large variation, which may be attributed to the quality of the raw materials used in its production (19).

Still, in relation to the toxic metals, Al was found in 100% of the samples, with concentrations within the range of 2,0 - 291 ppm.

Cd was detected in 82% of lipsticks from China with values up to 0,24 ppm, and in approximately 57% of European lipsticks, with values up to 0,09 ppm. Our results for Cd in Chinese samples – an average of 0,07 ppm - are consistent with other authors' discoveries of a mean result of 0,09 ppm of Cd for lipsticks available in Portuguese markets (34), but our European samples average concentration is way lower than that value – 0,012 ppm. Close to our findings towards European samples is the average value of 0,017 ppm obtained for Cd in this article (26). Both China and Europe averages are lower than the results of an assessment of Cd in cosmetic products used in Iran, with values within the range 4,08 - 60,20 ppm (20). Note that a different method was used.

Pb was present in approximately 73% of lipsticks from China and 78% from Europe, at a level of <LOD - 1,5 ppm and <LOD - 3,4 ppm, respectively. A test to 33 brands of lipsticks done by the Campaign for Safe Cosmetics, back in 2007, realize that 61% contained Pb, which is slightly lower than our findings (37). A European survey on the content of Pb in lip products, discovered an average Pb value of 0,58 – 0,88 ppm, depending on the lipstick color (6), which is higher than our average Pb value of 0,27 ppm and 0,42 ppm, for China and Europe samples. But a determination of lead in lipsticks sold in Iran determined a Pb content of 0,21 – 0, 46 ppm (15), which is close to our findings. Different from our results are the findings of an investigation of Pb in 25 lipsticks, although a different method is used, whose average Pb concentration is 1,91 ppm (4).

4.2. Statistical analysis results

There are statistically significant differences in the concentrations of Ba, Cd, Cu, and Li between the 2 origins. We could conclude that the average concentration of Ba, Cd, and Cu is higher in lipsticks from China, compared to Europe (graphics depicted in Figures 2, 3 and 4) and the contrary happens in the case of Li, where lipsticks from Europe have a greater average concentration (graphic in Figure 5).

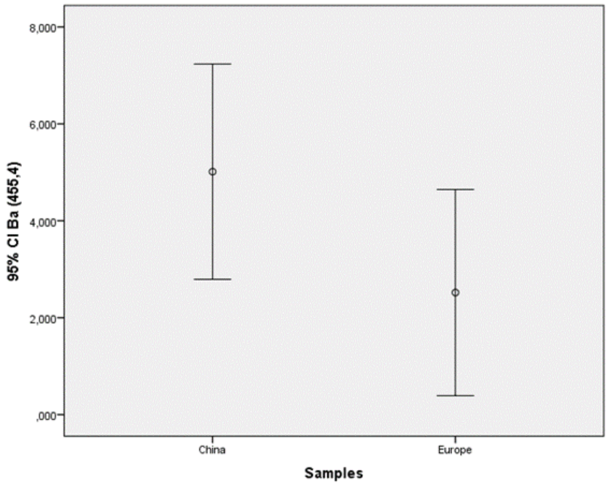

Figure 2. Statistic comparative study of Ba between Chinese and European samples. Average concentration of Ba is higher in China's samples.

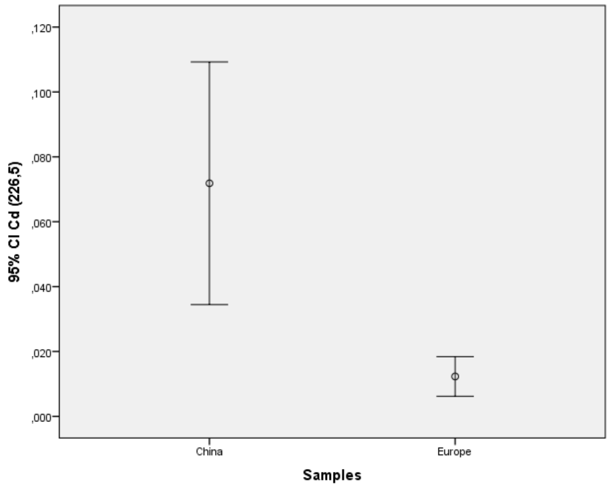

Figure 3. Statistic comparative study of Cd between Chinese and European samples. Average concentration of Cd is higher in China's samples.

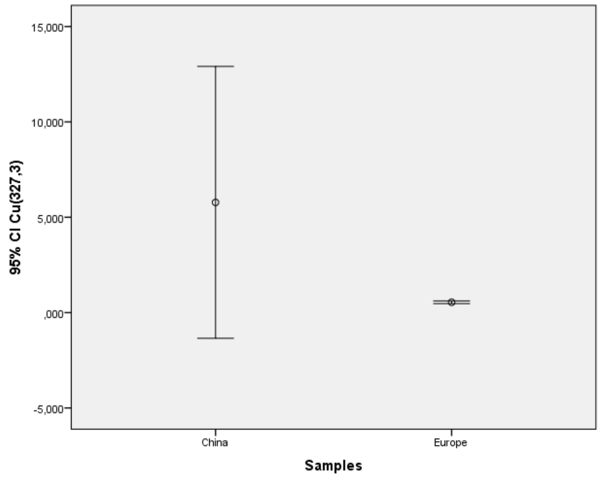

Figure 4. Statistic comparative study of Cu between Chinese and European samples. Average concentration of Cu is higher in China's samples.

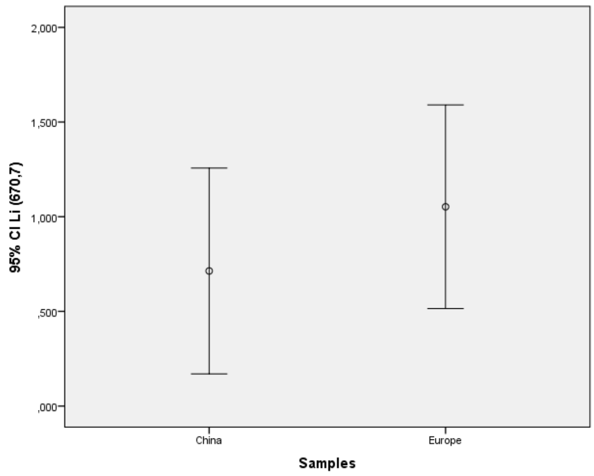

Figure 5. Statistic comparative study of Li between Chinese and European samples. Average concentration of Li is higher in Europe's samples.

4.3. Correlation studies

The correlations, either positive or negative, between the toxic and the other metals has also been a matter of study in our research, in which we could realize a positive correlation between the concentration of B/Cd and Ni/Cd in the samples from China (Figures 6 and 7) and between Cd/Fe, and K/Pb in the European samples (Figures 8 and 9). This means that as the concentration of a metal increases, so does the concentration of the other. Only $R^2 \geq 0,6$ have been considered in the described examples, as we can see in the graphics below.

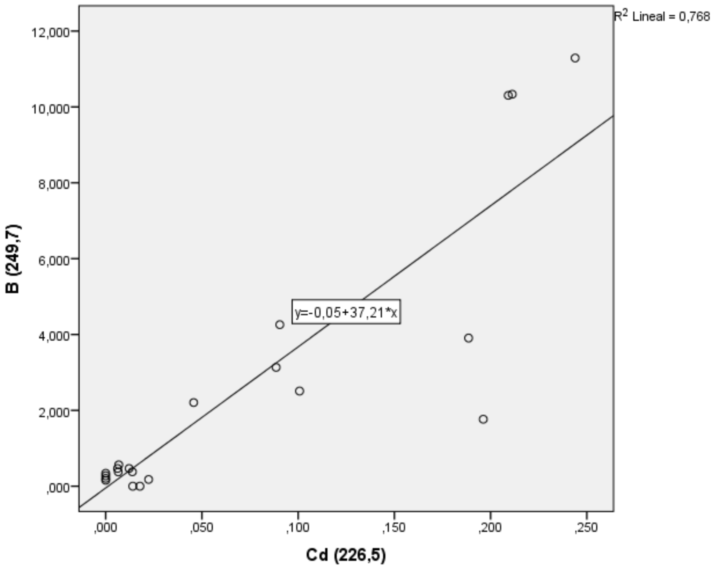

Figure 6. Correlational study between B and Cd in the 22 samples from China. A positive correlation between the microelement B and the toxic metal Cd is observed.

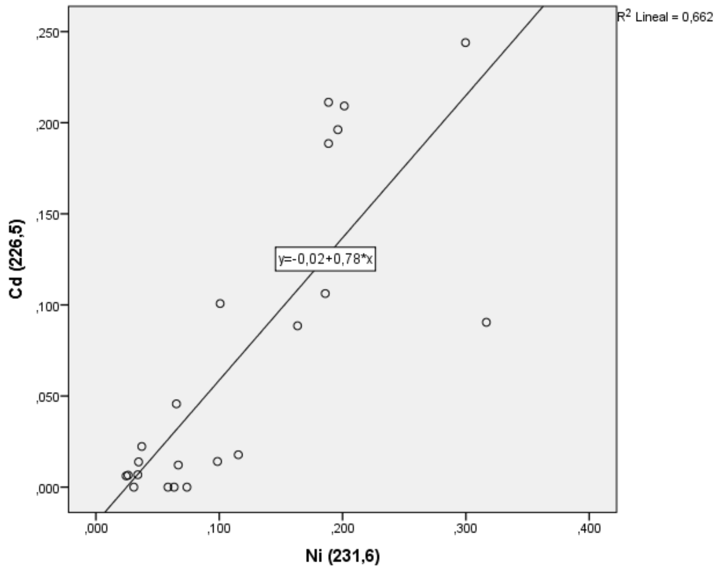

Figure 7. Correlational study between Cd and Ni in the 22 samples from China. A positive correlation between the microelement Ni and the toxic metal Cd is observed.

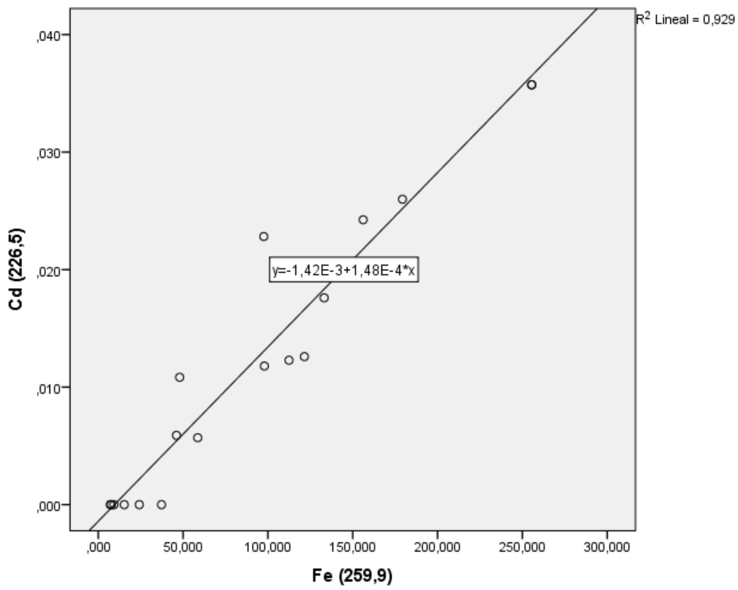

Figure 8. Correlational study between Cd and Fe in the 23 samples from Europe. A positive correlation between the microelement Fe and the toxic metal Cd is observed.

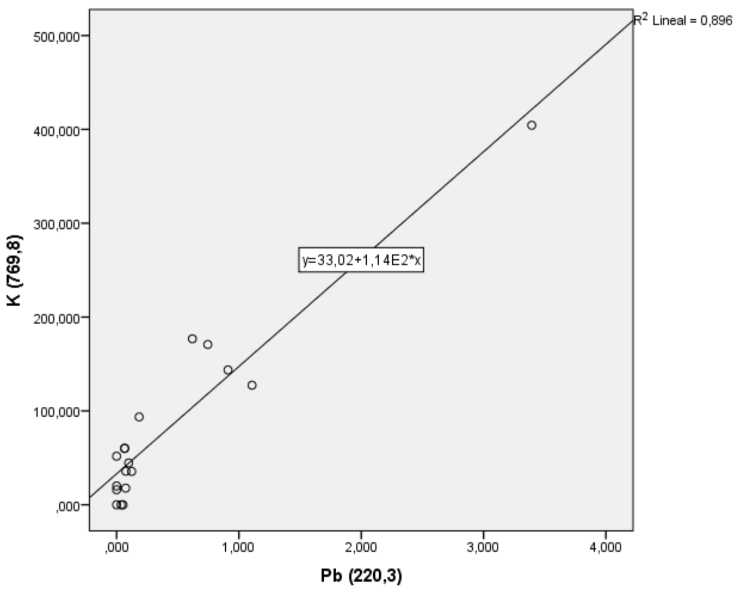

Figure 9. Correlational study between K and Pb in the 23 samples from Europe. A positive correlation between the macroelement K and the toxic metal Pb is observed.

4.4. Concentration of toxic metals in lipsticks samples and compliance with International Legislation

4.4.1. International Legislation

Respecting regulation, there is no globally harmonized system of safe permissible limits of heavy metals in cosmetics (8,13). Currently, in accordance with the European Regulation No. 1223/2009, many metals are banned as intentional ingredients, but they are not restricted as product impurities, since their presence as such is considered unavoidable, but, in turn, in conformity with article 3, it is requested that cosmetic products available on the market to be safe for human health when used under normal conditions (6). The Food and Drug Administration (FDA), in the US, has established concentrations up to a maximum value of 10 ppm of Pb in cosmetic pigments (53). Health Canada states the appropriate limits for Cd, 3 ppm, and Pb, 10 ppm, as impurities in cosmetic products (23). The Draft Guidance on Heavy Metal Impurities in Cosmetics, from Health Canada, states that toxicological properties and corresponding risk associated with other metals are considered less significant than for lead, cadmium, among others, and, accordingly, impurity limits in cosmetics for these metals have not been developed (36). The Ministry of Food and Drug Safety, in Korea, has specific limitations that are product dependent. Hence, in the case of makeup, in which group we think lipsticks belong, the limit for Pb is 10 ppm (23). Finally, the German Federal Office of Consumer Protection and Food Safety determined that metal levels, as impurities, in cosmetics, above 0,1 ppm for Cd, and 2 ppm for Pb were considered technically avoidable, in the newly revised limit (54).

4.4.2. Compliance with the International Legislation

A comparison was made of the concentrations obtained in this study with the levels established by the previous organizations. We did so, in 2 different parts: on one hand, we compared our results with Canada, Korea, and Germany limits, and we could conclude that neither the Cd nor Pb concentrations in the samples analyzed are above the Canadian limits and none surpass the Korean limit for Pb. However, a total of 6 samples (number 5, 7, 8, 15, 16 and 17) exceeded the German limits for Cd, all of them from China, and 1 sample (number 31) exceeded the limit for Pb. In this case, a European sample. This can be seen in the Attachments' point 7.1. and 7.2.

Then, we compared the values of the 3 toxic metals, Al, Cd, and Pb, for whom the risk assessment will be performed, with US and EU legislation, since we will use data from both entities in our assessment. Knowing this, eleven brands of lipstick from China and Europe samples were analyzed. Table 5 shows the Al, Cd, and Pb concentration detected in the 45 samples.

Table 5. Concentration of toxic metals in lipstick samples (mg kg^{-1})

China					Europe				
Nº	*Type of sample*	*Al*	*Cd*	*Pb*	*Nº*	*Type of sample*	*Al*	*Cd*	*Pb*
1	Purple Glitter/Brand 1	93,3	0,018	0,391	**23**	Red/Brand 7	74,5	0,00	0,00
2	Red/Brand 1	67,4	0,014	0,591	**24**	Rose/Brand 8	40,5	0,013	0,076
3	Red/Brand 2	38,4	0,00	0,045	**25**	Pink/Brand 8	62,9	0,00	0,099
4	Brown/Brand 2	1,98	0,007	0,033	**26**	Brown/Brand 8	33,4	0,012	0,074
5	Red/Brand 3	79,2	0,211	0,00	**27**	Brown Glitter/Brand 9	43,9	0,024	0,184
6	Brown/Brand 3	33,1	0,101	0,238	**28**	Pink/Brand 9	62,0	0,006	0,00
7	Dark Brown/Brand 3	80,6	0,209	0,00	**29**	Red/Brand 9	63,6	0,006	0,00
8	Purple/ Brand 3	71,8	0,244	0,00	**30**	Purple Glitter/Brand 9	50,0	0,026	1,107
9	Black/Brand 4	15,2	0,007	0,041	**31**	Purple Glitter/Brand 10	57,6	0,023	3,394
10	Pink/Brand 4	93,4	0,00	0,00	**32**	Light Pink Neon/Brand 10	3,61	0,00	0,052
11	Red/Brand 4	94,1	0,00	0,00	**33**	Dark Pink Neon/Brand 10	3,45	0,00	0,037
12	Purple/Brand 4	81,4	0,090	0,00	**34**	Pink Matte/Brand 10	57,7	0,00	0,745
13	Pink Magico/Brand 4	28,0	0,00	0,108	**35**	Red Matte/Brand 10	54,2	0,011	0,911
14	Pink Long Lasting/Brand 4	4,52	0,022	0,074	**36**	Purple/Brand 10	57,9	0,012	0,619
15	Pink/Brand 5	291	0,196	0,897	**37**	Pink/Brand 10	60,4	0,018	0,123
16	Pale Pink/Brand 5	111	0,189	0,862	**38**	Red/Brand 10	64,4	0,00	0,00
17	Brown/Brand 5	146	0,106	0,372	**39**	Light Brown/Brand 10	60,7	0,036	0,066
18	Brown/Brand 6	44,6	0,046	0,098	**40**	Dark Brown/Brand 10	61,6	0,089	0,00
19	Brown Long Lasting/Brand 6	7,34	0,014	0,083	**41**	Red Matte/Brand 11	60,1	0,00	0,143
20	Purple Long Lasting/Brand 6	70,8	0,089	1,458	**42**	Pink Acid/Brand 11	3,55	0,00	0,037
21	Blue Metallic Effect/Brand 6	57,8	0,012	0,467	**43**	Orange Matte/Brand 11	59,6	0,005	0,171
22	Gold Metallic Effect/Brand 6	40,4	0,006	0,160	**44**	Pink Matte/Brand 11	61,5	0,00	0,893
					45	Orange Acid/Brand 11	10,6	0,00	0,034
Mean±SD		70,5±61,8	0,07±0,08	0,27±0,38	*Mean±SD*		48,2±21,9	0,01±0,02	0,38±0,74
Min-Max		1,98-291	0 – 0,244	0 – 1,458	*Min-Max*		3,55 – 74,5	0 – 0,089	0 – 3,394

4.4.3. Concentration of aluminum

The mean concentration of Al in lipsticks from China was 70,5 mg·kg^{-1}, which is an identical result to that found by (23), where the concentration of Al in Korean lipsticks was 79,9 µg·g^{-1}. Lipsticks from Europe have an average amount of 48,2 mg·kg^{-1}. Neither European Union nor the United States have established maximum levels for Al in cosmetics, since many components used for the manufacture of these products incorporate Al, like “aluminum powder” and "aluminum lake dyes", for example *FD&C BLUE 1 Aluminum Lake* (33,55). The term “lake” refers to color additives usually used in food, drugs, and cosmetics. It contains aluminum oxide, which is reacted with coloring matter under aqueous conditions. These pigments are considered safe (47,56), since they are not soluble in water and stained by dispersion, thus, being regularly used when it is important to keep a color from "bleeding," as in lipstick (57,58). However, some unreacted aluminum oxide may also be present in the final product, which may presume a risk for the skin, although low, because of its dermabrasive properties (59).

4.4.4. Concentration of cadmium

The average Cd concentration of the lipsticks submitted to analysis was 0,07 mg·kg^{-1} for samples from China and 0,01 mg·kg^{-1} in samples from Europe. The highest concentrations were found in samples from brands 3 and 5, with values as high as 0,211 mg kg $^{-1}$, while in the rest of the brands the concentrations did not surpass 0,09 mg·kg^{-1}. The amount of Cd found in this study is lower than reported by (60–62), where the concentrations vary between 0,06 - 0,33 mg·kg^{-1}; 5,4 - 10,6 mg·kg^{-1}; and 1,83 - 412,23 mg·kg^{-1}, respectively. The FDA has not established a maximum concentration of Cd in cosmetics since they consider that the levels found in a variety of cosmetics products would not pose a health risk (63). The European Regulation (EC) No 1223/2009 (33), however, prohibits the use of cadmium and its compounds for the manufacture of cosmetic products. Hence, only 18% of the Chinese samples and 48% of the European samples meet the requirements of the European Regulation regarding Cd content.

4.4.5. Concentration of lead

The mean Pb concentrations detected in lipsticks were 0,27 mg·kg^{-1} in samples from China and, 0,38 mg·kg^{-1} in samples from Europe. The highest value found was 3,39 mg·kg^{-1} in sample 31. The results of the amount of Pb found in samples from China and Europe were slightly superior to the levels presented by (13,14), whose range of concentrations was 0,77 - 15,44 mg·kg^{-1} and 6,4 - 9,9 mg·kg^{-1}. In the case of Pb, the FDA has set a maximum level of 10 ppm (53), a concentration that is considered achievable by manufactures. The European regulation, however, as with the Cd, prohibits the presence of Pb and its compounds in cosmetics (33). This being said, on one hand, none of the samples of this study exceed the limits of 10 ppm established by the FDA, but, on the other hand, an approximately 72% of both China and Europe’s samples do not comply with the Regulation (EC) No 1223/2009 (33).

4.5. Human Health Risk Assessment

Since cosmetics are used for a prolonged period of time and are in contact with sensitive and thin areas of the skin, like the lips, the presence of heavy metals in this type of product has gained importance in recent years, because of the limited knowledge of its concentrations. Despite these concentrations may seems negligible if we compare them with water, food and air sources, their health toxicities should not be neglected.

4.5.1. SCCS'S health risk assessment

The health risk assessment evaluated under SCCS's guidelines is presented in Table 6. The highest SED was found in oral exposure for Al in lipstick from China. Our dermal SED for Cd and Pb differs from the SED deriving from dermal exposure in this study (7), which was 3,80 x 10^{-8} and 5,70 x 10^{-8} for Cd and Pb, respectively. The most worrying result, though, belongs to the MoS from oral exposure to Pb in lipsticks from China and Europe, both below the safety margin of 100 (40), so the possible health risks due to the presence of this metal in lipsticks should not be underestimated. It can be considered that the values obtained from the safety evaluation for Al and Cd are within those stipulated by the SCCS and that there is no risk to health, neither for oral or dermal exposure.

Table 6. Health risk assessment for the exposure to Al, Cd and Pb in lipstick samples from China and Europe under SCCS's guidelines

		China			**Europe**		
		Al	*Cd*	*Pb*	*Al*	*Cd*	*Pb*
EX		6,35E-02	6,30E-05	2,43E-04	4,34E-02	7,20E-05	3,42E-04
Dermal	*SED*	4,74E-06	1,34E-07	1,944E-07	3,24E-06	1,54E-07	2,74E-07
	MoS	2,64E7	1,41E5	1,47E4	3,86E7	1,23E5	1,04E4
Oral	*SED*	1,69E-04	8,40E-07	3,88E-05	1,16E-04	9,60E-07	5,47E-05
	MoS	7,39E6	2,26E4	73,6	1,08E7	1,98E4	52,3

"EX" units ($mg \cdot kg^{-1} \cdot day^{-1}$)
"SED" units ($mg \cdot kg^{-1} \cdot day^{-1}$)

4.5.2. US EPA's health risk assessment

The carcinogenic and non-carcinogenic risk assessments are summarized in Tables 7. and 8., respectively. Regarding the evaluation of carcinogenic risk, the highest "Total cancer risk" value corresponds to the oral evaluation of samples from Europe, which is $6{,}15x10^{-7}$. This result could be higher, since the cancer risk of Al was not considered, due to the lack of its slope factor. Despite this, the acceptable or tolerable risk for regulatory purposes is within the range of $10^{-6} – 10^{-4}$ (41), being the 10^{-4} the upper limit for acceptable risk of developing cancer (64), so there seems to be no risk to health. However, this result is very close to the range that the US EPA considers to be safe, so the possibility of risk to the population of high use of cosmetics should not be underestimated.

From the results obtained in the non-carcinogenic risk assessment, the highest results for HQ and HI are 0,090, corresponding to oral exposure to Al in lipsticks from China. In both cases, the results are below 1, so they could be considered safe because they show that there is no significant risk to health (41).

Table 7. Carcinogenic health risk assessment for the exposure to Al, Cd and Pb in lipstick samples from China and Europe under US EPA's guidelines

		Cancer risk assessment					
		Oral			**Dermal**		
		CDI	*Cancer risk*	*Total cancer risk*	*CDI*	*Cancer risk*	*Total cancer risk*
China	*Al*	3,60E-05	-	5,37E-07	1,99E-05	-	2,97E-07
	Cd	3,58E-08	5,36E-07		1,97E-08	2,96E-07	
	Pb	1,38E-07	1,17E-09		7,61E-08	6,47E-10	
Europe	*Al*	2,46E-05	-	6,15E-07	1,36E-05	-	3,39E-07
	Cd	4,09E-08	6,13E-07		2,25E-08	3,38E-07	
	Pb	1,94E-07	1,65E-09		1,07E-07	9,10E-10	

Table 8. Non-carcinogenic health risk assessment for the exposure to Al, Cd and Pb in lipstick samples from China and Europe under US EPA's guidelines

		Non-cancer risk assessment			
		Oral		**Dermal**	
		HQ	*HI*	*HQ*	*HI*
China	*Al*	0,090	0,090	0,050	0,050
	Cd	7,15E-05		3,95E-05	
	Pb	2,19E-04		1,21E-04	
Europe	*Al*	0,062	0,062	0,034	0,034
	Cd	8,17E-05		4,51E-05	
	Pb	3,08E-04		1,70E-04	

4.6. Intake Assessment

To make our research more useful, we decided to do an intake assessment, this is, calculate the contribution of the metals for which there are parameters such as TWI, TDI, RDI and Uls to the daily intake, accordingly to the concentrations we obtained for each of those in our samples. In order to assess the safety of the lipsticks, we used cosmetics' exposure data available in the L.J. Loretz *et al.* article (51) in which an average amount of 0,037g of lipstick is considered to be applied per application, and 0,087g is the average amount applied per day. Since the parameter's values are considered per day, we decided to focus on the average amount applied per day – 0,087g – to conduct our exercise.

We developed three scenarios: the first, where the average concentration of each metal, independently from the origin of the sample, was used to determine the contribution, in %, for the daily intake, for women and men aged 19 to 50 years. Unfortunately, we could not find parameters related to Co and Li; a second one, where the maximum detected concentration of each metal was used with the same purpose; and thirdly, for a "worst-case scenario" situation we picked the maximum detected concentration of each metal and the parameters for children with 5 years old, since at that age we considered that they can use lipsticks for some occasions, like Carnival, Halloween or Birthday parties. The adult body weight was set on 68,48 kg (38) and the children's body weight was set on 17,38 kg (65). The results are resumed in Table 10, 11 and 12.

Table 9. Intake Assessment for adults aged 19-50 years, using the mean metal concentrations

Metal	Parameter	Value	Source	Mean concentration (mg/kg)	Contribution(%)
Al	**TWI**	1 mg/kg bw/week	(48)	59,64	0,053
Cd	**$BMDL_5$**	0,357 µg/kg bw/day	(66)	0,01	0,004
Pb	**$BMDL_{01}$**	0,63 µg/kg bw/day	(50)	0,08	0,017
Ni	**TDI**	2,8 µg/kg bw/day	(67)	0,08	0,003
Sr		0,13 mg/kg bw/day	(68)	1,26	0,001
Ba		200 µg/kg bw/day	(69)	2,93	0,002
Cr	**RDI**	35 mg/day (men) 25 mg/day (women)	(70)	0,06	- -
Cu		1,1 mg/day		0,61	-
Fe		9 mg/day (men) 18 mg/day (women)		45,85	0,001 -
Zn		9,5 mg/day (men) 7 mg/day (women)		1,86	- 0,004
Mn		2,3 mg/day (men) 1,8 mg/day (women)		0,85	- 0,002
Mo		45 mg/day		0,02	-
Ca		1000 mg/day		159	-
Na		1500 mg/day		219	-
K		3100 mg/day		35,70	-
Mg		350 mg/day (men) 300 mg/day (women)		19,58	- -
B	**UL**	20 mg/day	(38)	0,71	-
V		1,8 mg/day		0,20	-

Note: Values of contribution inferior to 0,001% have been omitted

In terms of lipstick's contribution to the daily intake of the metals assessed, using the first scenario, the results do not seem to be concerning, since the highest contribution was 0,053% in the case of Al.

Table 10. Intake Assessment for adults aged 19-50 years, using maximum metal concentrations

Metal	Parameter	Value	Source	Maximum concentration (mg/kg)	Contribution (%)
Al	**TWI**	1 mg/kg bw/week	(48)	291	0,259
Cd	**$BMDL_5$**	0,357 µg/kg bw/day	(66)	0,24	0,085
Pb	**$BMDL_{01}$**	0,63 µg/kg bw/day	(50)	3,39	0,684
Ni	**TDI**	2,8 µg/kg bw/day	(67)	0,41	0,019
Sr		0,13 mg/kg bw/day	(68)	11,51	0,011
Ba		200 µg/kg bw/day	(69)	21,44	0,014
Cr	**RDI**	35 mg/day (men) 25 mg/day (women)	(70)	1,73	- -
Cu		1,1 mg/day		72,23	0,008
Fe		9 mg/day (men) 18 mg/day (women)		640	0,009 0,005
Zn		9,5 mg/day (men) 7 mg/day (women)		242	0,003 0,004
Mn		2,3 mg/day (men) 1,8 mg/day (women)		28,92	0,002 0,002
Mo		45 mg/day		93,32	-
Ca		1000 mg/day		2364	-
Na		1500 mg/day		3228	-
K		3100 mg/day		854	-
Mg		350 mg/day (men) 300 mg/day (women)		154	- -
B	**UL**	20 mg/day	(38)	11,29	-
V		1,8 mg/day		37,39	0,003

Note: Values of contribution inferior to 0,001% have been omitted

In this second scenario, a contribution of 0,684% to the daily intake was achieved for Pb. Comparing to water, air or food, a number of contribution for trace metals in lipsticks may look like a minimum fraction that can negatively affect human health, but, in our point of view, these negative effects should not be neglected, since cosmetics have been continuously applied to areas of the skin that are not only sensitive, such as the lips, but are also tissues with high blood perfusion, thus increasing the risk of percutaneous absorption. Furthermore, Pb has an oral absorption rate as high as 70% in fasting individuals, thus increasing our concerns (50).

Table 11. Intake Assessment for 5 years old children, using maximum metal concentrations

Metal	Parameter	Value	Source	Maximum concentration (mg/kg)	Contribution (%)
Al	**TWI**	1 mg/kg bw/week	(48)	291	1,102
Cd	**$BMDL_5$**	0,357 µg/kg bw/day	(66)	0,24	0,336
Pb	**$BMDL_{01}$**	0,5 µg/kg bw/day	(50)	3,39	3,394
Ni	**TDI**	2,8 µg/kg bw/day	(67)	0,41	0,073
Sr		0,13 mg/kg bw/day	(68)	11,51	0,044
Ba		200 µg/kg bw/day	(69)	21,44	0,054
Cr	**RDI**	15 mg/day	(70)	1,73	-
Cu		0,6 mg/day		72,23	0,060
Fe		8 mg/day		640	0,040
Zn		6 mg/day		242	0,020
Mn		1,5 mg/day		28,92	0,010
Mo		22 mg/day		93,32	0,002
Ca		700 mg/day		2364	0,002
Na		1200 mg/day		3228	0,001
K		1100 mg/day		854	-
Mg		120 mg/day		154	0,001
B	**UL**	6 mg/day	(71)	11,29	0,001

Note: Values of contribution inferior to 0,001% have been omitted

The extensive utilization of cosmetic products and the variable number of habits and practices of consumers are the head obstacles for an accurate evaluation of consumer exposure to cosmetics (31). However, we must take in consideration that the emphasis on individual beauty in media and magazines promote the use of cosmetics, such as lipsticks, not only by adolescents and women (16) but also by children, whose skin is characterized as thin, fragile, sensitive and has greater percutaneous absorption, which can lead to systemic toxicity (19). The current Centers for Disease Control and Prevention (CDC) guideline, for instance, states that there is no known safe blood lead level and even current low levels of exposure in children are linked to neurodevelopmental deficits (72) and in this last scenario, working with the values available for children, we encountered an approximately 3,4% contribution of Pb to the daily intake. In addition to what we explained before regarding the thin and sensitive area that lips represent, it's important to take in consideration that the oral absorption of Pb in children is even higher than in adults (44,50), hence we consider children as a vulnerable group in this study.

4.7. Discussion

Although initially, we had in mind to do a risk assessment including Ni and Cr, we realized that Ni, for instance, is poorly absorbed in the gastrointestinal tract – the HERAG states 0,05% to 0,3% as an oral absorption rate for this metal (73). Its carcinogenic action, on the other hand, is mainly provoked by occupational activity (74). It is, as well, an essential micronutrient, being part of both DNA and RNA, acting as a stabilizer of the tertiary structure of nucleic acids and proteins, not to mention its part as a structural component and co-factor of various enzymes (28) and, despite the fact that Ni is the most frequent cause of contact allergy, mainly presented as hand eczema, this usually happens not only to nickel-allergic individuals (75) but also if a combination of dermal exposure and *per os* ingestion of the element occurs, thus increasing sensitization and skin response to the metallic element. Hypersensitivity to Nickel can be occupational, as well (28). With all this combined, we did not perceive Ni as a worthy candidate to undergo a risk assessment. However, Nickel concentration above 1 ppm can cause contact dermatitis (35), so we found useful to see if the lipstick tested exceeded this level. This was not the case, since nickel's maximum concentration was 0,3 ppm.

About Cr, as mentioned before, the most common forms are Cr (III) and Cr (VI). Cr (III) is the most prevailing and exists naturally in the human body. Its biological function in glucose metabolism is already known. Cr (VI) however, is a recognized carcinogen, coming up as an industrial contaminant, in the chromate form (29) and has been associated with lung cancer (76). Since we could not distinguish, in our work, the two forms, we would not, therefore, been able to conduct an appropriate risk assessment study. Nonetheless, Cr maximum concentration is recommended to be 5 ppm, since it can act as an allergen (16), but in our work, the highest value was 1,7 ppm, and so, below the recommended maximum level.

Even though the concentrations of heavy metals have been studied in numerous articles, the clarification of how the described levels relate to possible adverse health risk assessment is demanding (23).

Regarding yet the risk assessment we conducted, we could not find a slope factor for Al, thus, we could not calculate its cancer risk. It would be important that future works came up with a slope factor for this element. The same note goes to parameters such as ADI, RDI, UL, TDI, and TWI for Co and Li, which could not be found.

Unfortunately, we didn't find any data related to percutaneous absorption of heavy metals in children, although there are some studies related to the transdermal patches used in pediatric, such as buprenorphine, clonidine, fentanyl, methylphenidate, nicotine, oestrogens, scopolamine and tulobuterol (77) and this one from Turpeinen *et al.*(78), which studied percutaneous absorption of hydrocortisone. Moreover, studies about quantitative estimates of the dermal absorption of aluminum, cadmium, and lead in the general population are too few. It could be a matter of deeper study.

Additionally, it would be important to assess As, Hg and Sb in this kind of cosmetics, since they are all recognized toxic metals. Sb, for example, is highly toxic, presenting several long-term effects (21). Unfortunately, our technique was not suitable to evaluate these metals. Besides, the market sampling we conducted was limited, thus we believe that if all lipsticks in the market were considered, the calculated health risks could be distinct.

As discussed previously, Health Canada stated that 100% of all cosmetics products have a positive result when tested for Ni; over 90% tested positive for Pb, and, on average, incorporate 4 out of 8 metals of concern, which are As, Be, Cd, Pb, Hg, Ni, Se and Ti (3). Using our results, we went to see if this claims are still updated and we could conclude that Ni was indeed present in all lipstick samples, with a minimum value of 0,03 ppm (see Table 4); Pb was present in approximately 76% of the samples tested (see Table 5), and so, in this aspect our findings are different from Health Canada statements, and, about the average number of samples which incorporate the metals of concern, we could not compare it properly, because we did not test As, Be, Hg, Se, and Ti. This could be a matter for further investigation in future studies.

Samples without batch information, namely 18, 21 and 22 of brand 6, pose a threat in terms of traceability, in the event of a recall, for example. If any defective sample needs a fast recall, the lack of this information is an obstacle, not to mention that the date of production, source of raw materials or even the machines used in the process of making the final product may all be related in the batch number.

We took the liberty to learn what is the industry doing to minimize impurities in cosmetics, and we could conclude that besides testing ingredients and the final product to verify if they meet certain specifications, some manufacturers also started to choose plant-based colorants instead of petroleum or even coal tar-based colorants to bypass raw material contaminants at some extent; others ask their supplier(s) to screen for impurities, and then choose the least contaminated ingredients, if possible, and in the USA, for instance, cosmetic producers can acquire certified ingredients that incorporate the lowest levels of harmful contaminants (21).

Our honest opinion is that to minimize any possible risk cosmetics may pose to human health, tighter cooperation must be done at international level, which involves toxicology specialists, in order to assess the safety of lipsticks and other personal care items and their wide share of ingredients on a constant basis.

To conclude, we think that this study and the data here disclosed are specifically significant if the absence of information on heavy metals present in lipsticks sold in Tenerife is considered.

5. Conclusions

The lipstick samples were collected in local markets and shopping centers of Tenerife and the concentration of 20 metals was quantified. Regarding the toxic metals, Al, Cd and Pb, a risk assessment was also performed.

Based on the FDA, the concentrations of metals that have stipulated maximum levels, in this type of cosmetics, did not exceed the limits.

In the case of the European Regulation No 1223/2009, most of the lipsticks did not comply with the requirements established by its guidelines with respect to Cd and Pb, since its presence in cosmetics is not allowed.

Concerning the Al limits, neither in the FDA nor in the European Regulation No 1223/2009 they have been established, because it is a metal widely used in the synthesis of "lake pigments". However, the presence of some unreacted aluminum oxide, a substance capable of dermabrasion, may also be present in the final product, which presumes a risk for the skin.

About the risk assessments conducted under the guidelines of both SCCS and US EPA, it can be concluded that the values from oral exposure to the Pb in lipsticks from China and Europe using the SCCS notes of guidance present a health risk, since an MoS below 100 was achieved.

The non-carcinogenic health risk assessment for the exposure to Al, Cd, and Pb in lipstick samples from China and Europe under US EPA's guidelines presented values of HQ and HI up to 0,090 in the case of Al. Even though at first sight there seems to be no risk, the presence of these dangerous metals in most of the lipsticks examined requires a precaution in their use by consumers, since these cosmetic products can constitute an important route of chronic exposure to these substances and, therefore, constitute a concern to health.

6. Bibliography

1. White IR, de Groot AC. Cosmetics and Skin Care Products. Contact Dermatitis. 2006;18(4):493–506.

2. Soares AR, Nascentes CC. Development of a simple method for the determination of lead in lipstick using alkaline solubilization and graphite furnace atomic absorption spectrometry. Talanta. 2013;105:272–7.

3. Orisakwe OE, Otaraku JO. Metal concentrations in cosmetics commonly used in Nigeria. Sci World J. 2013;2013.

4. Gunduz S, Akman S. Investigation of lead contents in lipsticks by solid sampling high resolution continuum source electrothermal atomic absorption spectrometry. Regul Toxicol Pharmacol [Internet]. 2013;65(1):34–7. Available from: http://dx.doi.org/10.1016/j.yrtph.2012.10.009

5. Selections S. News | Science Selections Metals in Lip Products. 2013;121(6):2013.

6. Piccinini P, Piecha M, Torrent SF. European survey on the content of lead in lip products. J Pharm Biomed Anal [Internet]. 2013;76(July):225–33. Available from: http://dx.doi.org/10.1016/j.jpba.2012.11.047

7. Marinovich M, Boraso MS, Testai E, Galli CL. Metals in cosmetics: An a posteriori safety evaluation. Regul Toxicol Pharmacol [Internet]. 2014;69(3):416–24. Available from: http://dx.doi.org/10.1016/j.yrtph.2014.05.005

8. Ullah H, Noreen S, Fozia, Rehman A, Waseem A, Zubair S, et al. Comparative study of heavy metals content in cosmetic products of different countries marketed in Khyber Pakhtunkhwa, Pakistan. Arab J Chem [Internet]. 2017;10(1):10–8. Available from: http://dx.doi.org/10.1016/j.arabjc.2013.09.021

9. Revert C, Martínez C, González-Weller D, Rubio C, Paz S, Gutiérrez AJ, et al. Trace element and toxic metal intake from the consumption of canned mushrooms marketed in Spain. Environ Monit Assess. 2018;190(4).

10. Obi G, Martincigh BS, Iwegbue CMA, Bassey FI, Tesi GO. Concentrations and exposure risks of some metals in facial cosmetics in Nigeria. Toxicol Reports. 2016;3:464–72.

11. Lemaire R, Bianco D Del, Garnier L, Beltramo JL. Determination of Lead in Lipstick by Direct Solid Sampling High-Resolution Continuum Source Graphite Furnace Atomic Absorption Spectrometry: Comparison of Two Digestion Methods. Anal Lett. 2013;46(14):2265–78.

12. Sani A, Gaya MB, Abubakar FA. Determination of some heavy metals in selected cosmetic products sold in kano metropolis, Nigeria. Toxicol Reports. 2016;3:866–9.

13. Zakaria A, Ho Y Bin. Heavy metals contamination in lipsticks and their associated health risks to lipstick consumers. Regul Toxicol Pharmacol [Internet]. 2015;73(1):191–5. Available from: http://dx.doi.org/10.1016/j.yrtph.2015.07.005

14. Gondal MA, Seddigi ZS, Nasr MM, Gondal B. Spectroscopic detection of health hazardous contaminants in lipstick using Laser Induced Breakdown Spectroscopy. J Hazard Mater. 2010;175(1–3):726–32.

15. Sharafi K, Fattahi N, Pirsaheb M, Yarmohamadi H, Fazlzadeh Davil M. Trace determination of lead in lipsticks and hair dyes using microwave-assisted dispersive liquid-liquid microextraction and graphite furnace atomic absorption spectrometry. Int J Cosmet Sci. 2015;37(5):489–95.

16. Al-Saleh I, Al-Enazi S. Trace metals in lipsticks. Toxicol Environ Chem. 2011;93(6):1149–65.

17. Salama AK. Assessment of metals in cosmetics commonly used in Saudi Arabia. Environ Monit Assess [Internet]. 2015;188(10). Available from: http://dx.doi.org/10.1007/s10661-016-5550-6

18. Kaličanin B, Velimirović D. A Study of the Possible Harmful Effects of Cosmetic Beauty Products on Human Health. Biol Trace Elem Res. 2016;170(2):476–84.

19. Batista ÉF, Augusto ADS, Pereira-Filho ER. Chemometric evaluation of Cd, Co,

Cr, Cu, Ni (inductively coupled plasma optical emission spectrometry) and Pb (graphite furnace atomic absorption spectrometry) concentrations in lipstick samples intended to be used by adults and children. Talanta [Internet]. 2016;150:206–12. Available from: http://dx.doi.org/10.1016/j.talanta.2015.12.011

20. Nourmoradi H, Foroghi M, Farhadkhani M, Dastjerdi MV. Assessment of lead and cadmium levels in frequently used cosmetic products in iran. J Environ Public Health. 2013;2013:2–7.

21. Bocca B, Pino A, Alimonti A, Forte G. Toxic metals contained in cosmetics: A status report. Regul Toxicol Pharmacol [Internet]. 2014;68(3):447–67. Available from: http://dx.doi.org/10.1016/j.yrtph.2014.02.003

22. Liu S, Katharine Hammond S, Rojas-Cheatham A. Concentrations and potential health risks of metals in lip products. Environ Health Perspect. 2013;121(6):705–10.

23. Lim DS, Roh TH, Kim MK, Kwon YC, Choi SM, Kwack SJ, et al. Non-cancer, cancer, and dermal sensitization risk assessment of heavy metals in cosmetics. J Toxicol Environ Heal - Part A Curr Issues [Internet]. 2018;81(11):432–52. Available from: https://doi.org/10.1080/15287394.2018.1451191

24. Al-Saleh I, Al-Enazi S, Shinwari N. Assessment of lead in cosmetic products. Regul Toxicol Pharmacol [Internet]. 2009;54(2):105–13. Available from: http://dx.doi.org/10.1016/j.yrtph.2009.02.005

25. González-Weller D, Rubio C, Gutiérrez AJ, Revert C, Ojeda I, Hardisson A, et al. Dietary Intake of Metals from Fresh Cage-Reared Hens' Eggs in Tenerife, Canary Islands. J Food Qual. 2017;2017:1–11.

26. Malvandi H, Sancholi F. Assessments of some metals contamination in lipsticks and their associated health risks to lipstick consumers in Iran. Environ Monit Assess. 2018;190(11).

27. Klotz K, Weistenhöfer W, Neff F, Hartwig A, Thriel C Van, Drexler H. The Health Effects of Aluminum Exposure. 2017;653–60.

28. Zambelli B, Ciurli S. Nickel and Human Health. 2013. 321-357 p.

29. Desmarias TL, Costa M. ScienceDirect Toxicology Mechanisms of chromium-induced toxicity. Curr Opin Toxicol [Internet]. 14(Iii):1–7. Available from: https://doi.org/10.1016/j.cotox.2019.05.003

30. Zeng F, Wei W, Li M, Huang R, Yang F, Duan Y. Heavy Metal Contamination in Rice-Producing Soils of Hunan Province , China and Potential Health Risks. 2015;(October):15584–93.

31. Coroama M, McNamara C, Leneveu-Duchemin MC, Tozer S, Hall B, Gibney M, et al. European consumer exposure to cosmetic products, a framework for conducting population exposure assessments. Food Chem Toxicol. 2007;45(11):2097–108.

32. Seaton A. Saturnism: an old story of poisoning. Qjm. 2014;107(6):501–2.

33. Pronko PP, VanRompay PA, Zhang Z, Nees JA. Reguation 1223/2009. 2009;(1223). Available from: https://link.aps.org/doi/10.1103/PhysRevLett.86.1387

34. Pinto E, Paiva K, Carvalhido A, Almeida A. Elemental impurities in lipsticks: Results from a survey of the Portuguese and Brazilian markets. Regul Toxicol Pharmacol [Internet]. 2018;95(April):307–13. Available from: https://doi.org/10.1016/j.yrtph.2018.04.009

35. Lead DOF, In N, Brands D, Lipsticks OF, Ih B, Qu AIN, et al. Issn : 2277 – 4998 Different Brands of Lipsticks Khalid a , Bukhari Ih *, Riaz M , Rehman G , Ain Qu , Bokhari Th , Rasool. Int J Biol Pharm Allied Sci. 2013;2(5):1003–9.

36. Rivas-Larrauri F, Yamazaki-Nakashimada MA. Lupus eritematoso sistémico: ¿es una sola enfermedad? Reumatol Clin [Internet]. 2016;12(5):274–81. Available from: http://dx.doi.org/10.1016/j.reuma.2016.01.005

37. Liu S, Hammond SK, Rojas-cheatham A. Concentrations and Potential Health Risks of Metals in Lip Products. 2013;121(6):705–10.

38. EC Pharmacology and Toxicology Research Article Exposure to Metals from the Consumption of Energy Drinks - Dietary Intake Assessment. 2019;7:691–701.

39. Luis González G. Metales esenciales y tóxicos en papas antiguas,papas importadas y otros tubérculoscomercializados en la isla de Tenerife :evaluación toxicológica [Internet]. 2014. Available from: http://www.tesisenred.net/handle/10803/482270

40. Committee S, Scientific Committee on Consumer Safety SCCS The SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and 10 th Revision. 2018.

41. Assessment PR. Risk Assessment Guidance for Superfund : Volume III - Part A , Process for Conducting Probabilistic Risk Assessment. III.

42. Hernandez E. Public Health Goal for Aluminum. 2001;(April).

43. Adams LS. Public Health Goal for Cadmium in Drinking Water. 2006;(December).

44. Health P, For G, In C, Water D. Chemicals in Drinking Water Public Health Goal for Lead in Drinking Water. 2009;(April).

45. GSI Chemical Database [Internet]. 2019 [cited 2019 May 19]. Available from: https://www.gsi-net.com/en/publications/gsi-chemical-database.html

46. Agencia Española de Medicamentos y Productos Sanitarios [Internet]. 2013 [cited 2019 May 20]. Available from: https://www.aemps.gob.es/laAEMPS/eventos/Cosmeticos/2013/J_evaluacion_seguridad_cosmeticos.html

47. Krewski D, Yokel RA, Nieboer E, Borchelt D, Harry J, Kacew S, et al. Human Health Risk Assessment for Aluminium , Aluminium Oxide , and Aluminium Hydroxide. Vol. 7404. 2011.

48. Food E, Authority S. On the Evaluation of a new study related to the bioavailability of. 2011;9(5):1–16.

49. Hartwig A, Jahnke G. Toxic metals and metalloids in foods [Internet]. Chemical contaminants and residues in food. Woodhead Publishing Limited; 233-249 p. Available from: http://dx.doi.org/10.1533/9780857095794.2.233

50. Panel E, Chain F. Scientific Opinion on Lead in Food 1. 2013;8(4):1–151.

51. Loretz LJ, Api AM, Barraj LM, Burdick J, Dressler WE, Gettings SD. Exposure data for cosmetic products : lipstick , body lotion , and face cream. 2005;43:279–91.

52. California Office of Environmental Health Hazard Assessment [Internet]. 2019 [cited 2019 May 23]. Available from: https://oehha.ca.gov/chemicals/lead-and-lead-compounds

53. U.S. Food and Drug Administration Draft Guidance on Lead in Cosmetic Lip Products [Internet]. [cited 2019 Sep 17]. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/draft-guidance-industry-lead-cosmetic-lip-products-and-externally-applied-cosmetics-recommended

54. Prühs N, Schöberl K, Habernegg R. Analytik von kosmetischen Mitteln. Dtsch Leb. 2017;113(6):254–8.

55. Summary of Color Additives for Use in the United States [Internet]. U.S. Food and Drug Administration. 2019 [Internet]. 2019 [cited 2019 Sep 13]. Available from: https://www.fda.gov/industry/color-additive-inventories/summary-color-additives-use-united-states-foods-drugs-cosmetics-and-medical-devices#ftnote6

56. Becker LC, Boyer I, Bergfeld WF, Belsito D V, Hill RA, Klaassen CD, et al. Safety Assessment of Alumina and Aluminum Hydroxide as Used in Cosmetics. 2016;35(Supplement 3):16–33.

57. Food and Agriculture Organization [Internet]. 2019 [cited 2019 Sep 11]. Available from: http://www.fao.org/fileadmin/user_upload/jecfa_additives/docs/monograph3/additive-013.pdf

58. U.S. Food and Drug Administration Color Additives and Cosmetics: Fact Sheet [Internet]. [cited 2019 Sep 12]. Available from: https://www.fda.gov/industry/color-additives-specific-products/color-additives-and-cosmetics-fact-sheet

59. Tan M, Spencer JM, Pires LM, Ajmeri J, Skover G. The Evaluation of Aluminum Oxide Crystal Microdermabrasion for Photodamage. 2001;943–9.

60. Zakaria A, Ho Y Bin. Heavy metals contamination in lipsticks and their associated health risks to lipstick consumers. Regul Toxicol Pharmacol [Internet]. 2015;73(1):191–5. Available from: http://dx.doi.org/10.1016/j.yrtph.2015.07.005

61. Gondal MA, Seddigi ZS, Nasr MM, Gondal B. Spectroscopic detection of health hazardous contaminants in lipstick using Laser Induced Breakdown Spectroscopy. 2010;175:726–32.

62. Nkansah MA. Determination of lead and cadmium contents in lipstick and their potential health risks to consumers. J Consum Prot Food Saf [Internet]. 2018;0123456789. Available from: https://doi.org/10.1007/s00003-018-1180-y

63. U.S. Food and Drug Administration Arsenic, Cadmium, Chromium, Cobalt, Lead, Mercury, and Nickel Content [Internet]. 2019 [cited 2019 Sep 15]. Available from: https://www.fda.gov/cosmetics/potential-contaminants-cosmetics/fdas-testing-cosmetics-arsenic-cadmium-chromium-cobalt-lead-mercury-and-nickel-content

64. Antoine JMR, Fung LAH, Grant CN. in Jamaica. Toxicol Reports [Internet]. 2017;4(March):181–7. Available from: http://dx.doi.org/10.1016/j.toxrep.2017.03.006

65. Portier K, Tolson JK, Roberts SM. Body Weight Distributions for Risk Assessment. 2007;27(1).

66. Panel E, Chain F. Statement on tolerable weekly intake for cadmium 1. 2011;9(2).

67. Panel E, Chain F. EFSA CONTAM Panel (EFSA Panel on Contaminants in the Food Chain), 2015 . Scientific Opinion on the risks to public health related to the presence of nickel in food and drinking water Scientific Opinion on the risks to public health related to the presence of nickel in food and drinking water 1. 2015;

68. Advice T, Howe P, Wood M. Concise International Chemical Assessment Document 77.

69. Risks E. Scientific Committee on Health and Environmental Risks SCHER Assessment of the Tolerable Daily Intake of Barium. 2012;(March).

70. Diet I. Actividad Dietética Dietética. 2010;14(4):196–7.

71. U.S. Department of Agriculture [Internet]. [cited 2019 May 28]. Available from: https://www.nal.usda.gov/fnic/dri-tables-and-application-reports

72. D.C. B. Very low lead exposures and children’s neurodevelopment. Curr Opin Pediatr [Internet]. 2008;20(2):172–7. Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L351365708%0Ahttp://dx.doi.org/10.1097/MOP.0b013e3282f4f97b

73. Uptake G, Of C, Models T. HERAG 04 Gastrointestinal Uptake and Absorption , Health Risk Assessment Guidance for Metals Fact Sheet. 2007;(August).

74. Pavela M, Uitti ÃJ, Pukkala E, Phd P. Cancer Incidence Among Copper Smelting and Nickel Re fi ning Workers in Finland. 2016;1–9.

75. Ahlström MG, Thyssen JP, Wennervaldt M, Johansen JD. Nickel allergy and allergic contact dermatitis : A clinical review of immunology , epidemiology , exposure , and treatment. 2019;(May):4–7.

76. Suh M, Wikoff D, Lipworth L, Goodman M, Fitch S, Mittal L, et al. Critical Reviews in Toxicology Hexavalent chromium and stomach cancer : a systematic review and meta-analysis. Crit Rev Toxicol [Internet]. 2019;0(0):1–20. Available from: https://doi.org/10.1080/10408444.2019.1578730

77. Delgado-charro MB, Guy RH. Effective use of transdermal drug delivery in children. Adv Drug Deliv Rev [Internet]. 2013; Available from: http://dx.doi.org/10.1016/j.addr.2013.11.014

78. Turpeinen M, Lehtokoski-lehtiniemi E, Leisti S, Salo OP. Percutaneous Absorption of Hydrocortisone During and After the Acute Phase of Dermatitis in Children. (4):276–80.

7. Attachments

7.1. Macroelement and microelement's concentrations in the 22 lipstick samples from China (mg kg^{-1})

Nº	B	Ba	Ca	Co	Cr	Cu	Fe	K	Li	Mg	Mn	Mo	Na	Ni	Sr	V	Zn
1	<LOD	8,748	562	<LOD	0,355	0,488	82,68	854	1,883	65,54	1,377	42,36	1581	0,115	2,291	0,355	1,989
2	<LOD	3,041	1063	<LOD	0,380	2,366	11,19	427	2,119	54,21	0,190	1,338	2816	0,099	2,858	0,345	0,613
3	0,156	<LOD	29,45	<LOD	0,065	0,311	1,051	<LOD	<LOD	<LOD	0,123	0,078	57,86	0,058	0,208	<LOD	0,422
4	0,378	1,252	45,92	<LOD	<LOD	0,352	45,85	<LOD	<LOD	<LOD	0,248	0,020	89,36	0,026	0,326	0,104	0,320
5	10,33	6,307	1388	0,158	0,234	1,064	<LOD	<LOD	0,317	32,59	0,852	0,468	296,5	0,189	3,123	0,143	1,471
6	2,51	8,984	386	0,119	0,000	1,987	319	80,3	0,714	24,36	5,833	<LOD	225,3	0,101	1,071	0,101	2,344
7	10,30	5,555	1588	0,256	0,116	0,860	<LOD	<LOD	0,287	52,68	26,57	0,139	205,3	0,201	0,542	0,155	1,828
8	11,29	6,203	2133	0,237	0,251	1,157	<LOD	77,4	0,195	93,39	28,92	<LOD	366,6	0,300	1,833	0,216	4,774
9	0,563	12,56	60,68	0,095	<LOD	0,333	60,62	<LOD	<LOD	13,37	13,17	0,020	80,10	0,034	0,462	0,088	0,414
10	0,275	20,38	833	<LOD	0,359	0,665	21,12	264	0,412	27,78	1,035	0,158	703,4	0,063	11,51	0,349	0,856
11	0,341	10,06	614	<LOD	<LOD	0,646	9,32	<LOD	<LOD	<LOD	0,295	0,655	359,8	0,074	2,685	0,065	8,838
12	4,26	<LOD	48,99	0,369	0,219	29,92	640	<LOD	<LOD	<LOD	16,88	0,294	222,3	0,317	2,133	0,196	241,9
13	0,207	2,044	492	0,023	<LOD	0,914	8,99	<LOD	0,376	25,28	0,123	<LOD	70,84	0,031	0,830	0,077	1,859
14	0,178	3,435	1881	0,126	<LOD	1,175	2,89	74,4	0,312	<LOD	0,126	0,022	210,4	0,037	7,139	0,164	35,84
15	1,77	<LOD	583	0,056	<LOD	3,083	8,04	<LOD	0,897	82,40	0,729	<LOD	1110	0,196	4,316	0,252	5,101
16	3,91	7,085	331	0,108	<LOD	2,290	501	<LOD	<LOD	69,23	1,320	<LOD	1099	0,189	2,963	0,458	3,502
17	4,65	4,756	142	0,106	<LOD	1,807	566	<LOD	2,683	<LOD	2,816	<LOD	470,2	0,186	1,355	0,266	1,966
18	2,21	1,671	1423	0,026	0,085	0,463	345	178	0,098	19,58	8,486	0,046	2820	0,065	10,57	0,189	0,392
19	0,381	<LOD	171	0,000	<LOD	0,408	35,44	<LOD	<LOD	15,71	1,294	<LOD	141,2	0,035	1,232	0,104	0,948
20	3,13	2,847	2364	0,129	0,368	0,620	608	324	0,361	133,5	9,809	93,32	2357	0,163	8,038	0,443	8,311
21	0,467	<LOD	36,54	0,036	<LOD	72,23	49,83	78,9	<LOD	<LOD	1,730	12,44	262,8	0,067	0,649	37,39	0,662
22	0,467	5,375	30,77	0,055	1,732	4,023	38,21	125	5,043	<LOD	0,516	0,025	177,5	0,025	1,247	0,227	1,628

Note: <LOD means inferior to the limit of detection of the equipment

7.2. Macroelement and microelement's concentrations in the 23 lipstick samples from Europe (mg kg^{-1})

Nº	B	Ba	Ca	Co	Cr	Cu	Fe	K	Li	Mg	Mn	Mo	Na	Ni	Sr	V	Zn
23	0,696	12,41	159,3	0,021	0,062	0,634	24,20	51,78	0,455	30,34	0,524	0,000	172,4	0,055	2,255	0,179	2,096
24	1,158	<LOD	75,55	<LOD	<LOD	0,466	121,5	35,70	0,976	<LOD	0,806	0,013	183,2	0,031	0,724	0,623	0,346
25	0,339	<LOD	95,04	0,019	0,056	0,469	15,30	44,56	3,172	12,84	0,531	<LOD	216,0	0,062	0,685	0,235	1,006
26	0,891	<LOD	138,9	0,025	<LOD	0,356	112,4	17,76	0,879	<LOD	1,954	<LOD	130,3	0,037	1,339	1,008	0,412
27	1,663	<LOD	366,1	0,097	0,058	0,330	156,1	93,58	0,480	146,4	9,067	<LOD	177,9	0,286	1,658	0,204	0,204
28	0,768	0,694	129,2	0,017	0,080	0,660	58,63	<LOD	0,342	94,49	0,546	0,023	193,5	0,034	0,507	0,159	0,268
29	0,795	<LOD	232,1	<LOD	0,088	0,507	46,08	20,03	0,348	126,1	0,707	1,320	245,7	0,088	0,807	0,194	1,155
30	0,790	2,926	1538	0,031	0,192	0,437	179,3	127,3	0,161	154,4	11,49	0,016	894,0	0,099	8,420	0,172	0,281
31	3,057	2,316	912,6	0,051	<LOD	0,633	97,54	404,4	3,052	47,97	3,166	<LOD	3228	0,080	2,504	0,542	0,907
32	0,407	3,006	0,000	<LOD	0,080	0,407	7,056	<LOD	0,155	<LOD	0,184	0,109	<LOD	<LOD	0,287	0,086	30,29
33	0,340	1,600	26,45	<LOD	0,080	0,568	9,207	<LOD	0,216	<LOD	0,204	<LOD	61,67	0,043	0,229	0,000	34,66
34	0,381	<LOD	127,3	0,016	0,087	0,495	37,26	170,8	0,359	11,91	0,234	0,027	84,31	0,071	1,398	0,392	141,4
35	<LOD	4,884	513,3	0,054	0,276	0,477	47,97	143,6	1,014	151,8	1,377	1,182	623,4	0,314	0,650	0,314	3,767
36	3,721	2,919	801,9	0,024	0,065	0,607	97,88	176,9	1,545	19,69	0,879	0,018	1557	0,029	4,446	0,548	0,772
37	1,132	<LOD	108,5	0,047	0,059	0,651	133,2	35,55	0,282	17,42	0,440	<LOD	339,6	0,076	1,472	0,393	9,737
38	0,705	14,59	155,0	0,018	0,188	0,930	7,721	15,93	0,164	26,14	0,328	0,085	324,1	0,116	1,167	0,164	1,411
39	1,858	<LOD	34,60	0,060	<LOD	0,572	255,5	60,15	2,674	14,71	7,563	<LOD	101,2	0,077	0,584	1,048	8,278
40	4,332	<LOD	81,18	0,243	0,119	0,705	598,5	11,44	0,083	23,52	10,37	<LOD	219,2	0,415	1,073	2,341	0,836
41	0,713	7,281	529,5	0,015	0,193	0,474	36,35	280,5	0,586	27,60	0,316	0,031	175,7	0,117	7,026	0,219	26,07
42	0,568	17,40	23,51	<LOD	<LOD	0,253	19,00	16,16	0,154	<LOD	0,099	<LOD	47,51	0,086	0,475	0,068	23,38
43	0,792	3,662	99,73	0,034	0,073	0,318	71,86	440,9	<LOD	19,41	1,374	0,078	870,2	0,166	1,242	0,166	20,04
44	0,383	21,34	117,0	0,010	0,091	0,288	18,61	201,8	0,383	11,65	0,217	0,015	37,73	0,061	1,256	0,161	10,09
45	0,420	21,44	24,05	<LOD	0,045	0,284	10,38	18,61	0,216	<LOD	0,136	<LOD	47,76	0,034	0,533	0,028	19,85

Note: <LOD means inferior to the limit of detection of the equipment