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ORIGINAL ARTICLE

Carcinogenic, Non-carcinogenic and Dermal Sensitization Risk Assessment of Heavy Metals in Liquid and Solid Lipsticks Highly Used in Kashan, Iran

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KEYWORDS

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ABSTRACT: The present study aimed to investigate the levels of lead (Pb), nickel (Ni), cadmium (Cd), and chromium (Cr) in highly used lipsticks in Kashan, Iran. The average concentrations of metals in lipsticks were lower than the maximum admissible limits determined by the Food and Drug Administration (FDA). The highest and lowest levels of systematic exposure dose (SED) were found for Cr and Pb metals, respectively. However, the SEDs of all metals were less than the reference doses (RFD). The hazard index (HI) of non-carcinogenic risk for all metals was less than 1 and there is no threat to consumers in the concentrations of the metals in the lipsticks. Also, for all metals, the margin of exposure (MoE) and the lifetime cancer risk (LCR) were higher and lower than 10^4 and 10^{-6}, respectively. Therefore, the possibility of carcinogenic risks of these metals due to the use of lipsticks is low. The results showed that the dermal sensitization quantitative risk assessment (SQRA) for Ni was greater than 1 and no dermal sensitization risk is observed.

INTRODUCTION

Over the past few decades, there has been significant progress in the cosmetic industry, which includes the production of various kinds of cosmetics [1, 2]. One of the most popular cosmetics is lipstick, whose primary ingredients are wax, oil, alcohol, and pigment. The highest consumptions of cosmetics were observed in the Middle East, Iran, and Saudi Arabia so that Iranian women annually pay about 1 billion dollars for cosmetics [1, 3].

The US Food and Drug Administration (FDA) and the European Union's Restriction on Hazardous Substances (ROHS) directive have recently reported that some cosmetic materials used by humans contain hazardous substances. Owing to this fact, there is a growing concern

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that some of the cosmetic products used by humans contain hazardous substances that are harmful to health [4, 5].

Many studies have shown that hygienic cosmetic products contain high concentrations of heavy metals (Table1) [6-15]. Pb is not one of the components of lipstick but it is present as impurities in color additives [1, 2]. Exposure even to low concentrations of Pb can cause impairment in hearing, learning, as well as adverse effects on the central nervous system, genital, liver, and kidney systems [16, 17].

Cadmium (Cd) is also a heavy metal present in cosmetics. If the human body is directly exposed to this metal, it can elevate blood pressure and also cause renal dysfunction and prolonged exposure to it results in lung obstruction disease [18, 19]. Chromium VI (Cr VI) is also used as a colorant element in lipstick, and hair dye. Breathing high levels of it can cause the stimulation of nasal cover, asthma, shortness of breath and wheezing, and skin contact can cause skin ulcers and allergic reactions, including redness and swelling of the skin [20].

Exposure assessment techniques available today can significantly affect the improvement of the quality of epidemiological studies, health risks assessment, identification of safe exposure levels, as well as showing the capability to be used as a step in controlling contaminants [21]. These methods have been widely utilized by many researchers in the literature on the assessment of the harmful health effects possible from exposure to various contaminated products [22-24].

Several studies have evaluated the carcinogenic and non-carcinogenic risks of heavy metals in cosmetics. A study showed that the non-carcinogenic HI and LCR for total heavy metals in Alexandria city in Egypt were 7×10^{-4} and 0.0098 for lipsticks, respectively. Both indicators were within safe ranges [25].

A previous study reported that the concentrations of Cr, Ni, Pb, and Cd for some kinds of lipsticks were in the ranges of 0-0.32, 0-0.59, 0-9.28, and 0-0.009 µg g^{-1}, respectively. The Margin of Safety (MoS) indicator was higher than 100 and the non-carcinogenic HI was less than 1 both of which were in a safe range. Moreover, the MoE value was higher than 10^4 and the non-carcinogenic risk was between 10^{-4} to 10^{-6} both of which were also in a safe range [26].

Since humans are exposed to significant amounts of non-manageable cosmetics and personal care products, the safety of these products should be assessed precisely before being used. Therefore, this research aimed to investigate the amount of concentration, and the carcinogenic, non-carcinogenic, and dermal sensitization risk assessment of heavy metals for solid and liquid lipsticks highly used in Kashan, Iran. Therefore, the results of this study may provide some insight into heavy metal contamination in solid and liquid lipsticks and can be beneficial for inhabitants in formulating protective procedures in decreasing heavy metal contamination in cosmetic products and reducing the possible health risks to the population. Also, these results can be used as a foundation for comparison to other regions, both in Iran and worldwide.

MATERIALS AND METHODS

Sampling and Analysis of Heavy Metals

In this cross-sectional study carried out in the period from May 2017 to November 2017, according to the obtained data from the cosmetics department of Kashan, 10 highly consumed brands of solid lipsticks and 6 highly consumed brands of liquid lipsticks were identified. 3 samples were prepared from each brand and each sample was purchased from one store. To analyze the concentrations of heavy metals (Pb, Ni, Cd, and Cr), samples were transferred to the research laboratory of the Faculty of Health, Kashan University of Medical Sciences.

The acid digestion was performed according to the previous research [27]. A multi-element standard containing 23 elements was prepared from Merck ICP standards (1000 ppm). Deionized water (Electrical conductor< 0.1 µs cm^{-1}) was purified with the system (Dionizer model R.200.M) and obtained immediately before being used for the preparation of all solutions. Concentrated nitric acid and hydrogen peroxide were obtained from Merck (Darmstadt, Germany). Plastic bottles and glassware were all soaked in 20% v v^{-1} HNO_3 for 24 hours, rinsed several times with Milli-Q water, and dried at room temperature. Finally, heavy metals were determined by ICP-OES; inductively coupled plasma optical emission spectrometry (Perkin

Elmer Optima 2100 DV model, USA) with device power to create a radio frequency of 1300 watts, 15 L min^{-1} plasma gas flow rate, 0.2 L min^{-1} auxiliary gas flow rate, and 0.8 L/minute Nebulizer gas flow rate. The concentrations of the abovementioned heavy metals in the samples were measured based on a standard curve and their contents in the cosmetic product were reported in µg/g.

Non-Carcinogenic Risk Assessment

Margin of safety (MoS): To evaluate the non-carcinogenic risk assessment, the MoS formula was used. According to WHO, if the MoS of a substance is less than 100, that substance is harmful to health.

$$MoS= NOAEL/SED \qquad (1)$$

Where, NOAEL (no observed adverse effect level) is the highest dose at which there was not any observed toxic or adverse effect; SED (systemic exposure dose) of chemical material is the amount expected to enter the bloodstream. These two indices were calculated with formulas 2 and 3, respectively:

$$NOAEL\ (mg.\ kg\ bw^{-1}.\ day^{-1}) = RFD\times UF\times MF \qquad (2)$$

$$SED\ (mg\ kg\ bw^{-1}.\ day^{-1}) = (C\times AA\times SSA\times F\times RF\times BF/BW) \times 10^{-3} \qquad (3)$$

Where, RFD denotes reference doses ($Pb=4\times10^{-3}$, $Cd=1\times10^{-3}$, $Cr=3\times10^{-3}$ and $Ni=2\times10^{-2}$ mg. kg bw^{-1}. day^{-1}) [28]; UF is the uncertainty factor and equals to 100; MF is the modifying factor and equals to 1; C is observed concentrations of heavy metals in cosmetic products in mg kg^{-1}; AA is the amount of lipstick consumption per day (0.057 g d^{-1}); SSA is the area of skin exposed to lipstick (4.8 cm^2); F is the frequency of cosmetics consumption per day (2 times in a day); RF is the retention factor (1); BF is the access bioavailability factor (10^{-3}); BW denotes human body weight (70 kg) in this study [29].

Hazard quotient (HQ)

HQ is the overall potential for non-carcinogenic health effects caused by Pb, Cd, Ni and Cr in each cosmetic sample. It is safe if below 1; otherwise, it is considered unsafe.

$$HQ= SED/RFD \qquad (4)$$

Hazard index (HI)

HI is the sum of HQ for cosmetic samples. It is safe if below 1.

$$HI=HQ_{Pb}+HQ_{Ni}+H_{Cr}+HQ_{Cd} \qquad (5)$$

Carcinogenic Risk Assessment

Margin of exposure (MoE)

MoE is a term used to assess the risk of carcinogenic substances. If the MoE of a substance is less than 10000, that substance is harmful to health.

$$MoE=BML_{10}/SED \qquad (6)$$

Where, BML10 (benchmark dose lower limit) is the dose lower limit of a substance which causes to create a response. This dose is 0.14, 0.28, 0.00063 and 0.67 mg.kg day^{-1} for Cr, Ni, Pb and Cd, respectively.

Lifetime cancer risk (LCR)

LCR is the cancer risk in the average of lifetime and calculated by using the following formula. The values between 10^{-4} to 10^{-6} are considered safe [26].

$$LCR = SED\times CSF \qquad (7)$$

Where, CSF (cancer slope factor) is the higher range of probability of carcinogenicity of an individual in response to each received dose unit of chemicals in the average of their lifetime. The values of this factor are reported as 0.5, 0.91, 0.0085 and 6.7 mg.kg day^{-1} for Cr, Ni, Pb and Cd, respectively [25, 30, 31].

Quantitative risk assessment (QRA) of dermal sensitivity

No expected sensitizing induction level (NESIL)

NESIL is the evaluation of the dose response and calculated using the following formula. The results are expressed based on the dose rate per unit area of μg $cm^{2\ -1}$.

$$\log_{10} NESIL = 1.16 \log_{10} EC_3 - 0.64 \quad (8)$$

Where, EC_3 is the distribution of the sensitivity of the material from the weak to the extreme sensitivities. It was calculated by using the following formula. EC3% for Ni is 2.5%, and one of the materials with medium sensitization.

$$EC_3 = EC_3\% \times 0.025 \times 1000000/100 \times 1 \quad (9)$$

Acceptable exposure level (μg $cm^{2\ -1}$) (AEL)

AEL is the exposure level to a chemical compound that is within the mandated safe level. For this purpose, the following formula is used.

$$AEL = NESIL/SAF \quad (10)$$

Where, SAF (susceptibility or uncertainty assessment factor) is the factors such as how to use, individual human factors, the human population such as age, sex, genetics, ethnicity, etc., which affects the sensitivities response to chemicals.

Consumer exposure level (μg $cm^{2\ -1}$ d^{-1}) (CEL)

It indicates how the consumer encounters cosmetic products.

$$CEL = C \times AA \times F \times 10^6/SSA \quad (11)$$

Where, C is the concentration of metal in the facial cosmetic product (mg kg^{-1}); AA is the amount of consumption for every use and for lipstick, it is 0.057g; F is daily consumption frequency and for lipstick, it was 2 times a day; SSA is the skin surface area on which the products are applied (lip surface area is 4.8 cm^2) [32].

Risk determination

It is the last stage of quantitative risk assessment. For this purpose, the following formula is employed.

$$\text{Risk determination} = AEL/CEL \quad (12)$$

If this ratio is greater than 1, it indicates the safety of the exposure [32-34].

Statistical analysis

All data, with three replications, were expressed as mean ± standard deviation (SD). The data were analyzed by Kolmogorov-Smirnov, Leven, and Mann-Whitney tests. The T-test and analysis of variance (ANOVA) were used for binary comparisons, by using SPSS version 16 (SPSS Inc., Chicago, IL, USA). P-values <0.05 were considered significant.

RESULTS

The average concentrations of heavy metals of Pb, Cd, Cr and Ni in highly consumed liquid and solid lipsticks in Kashan, Iran, are shown in Figure 1. The highest and the lowest amounts of metals in liquid lipstick samples were observed for Pb and Cd, respectively. However, there was no significant difference between the lipstick types in terms of the concentration of each metal ($P_{value}>0.05$).

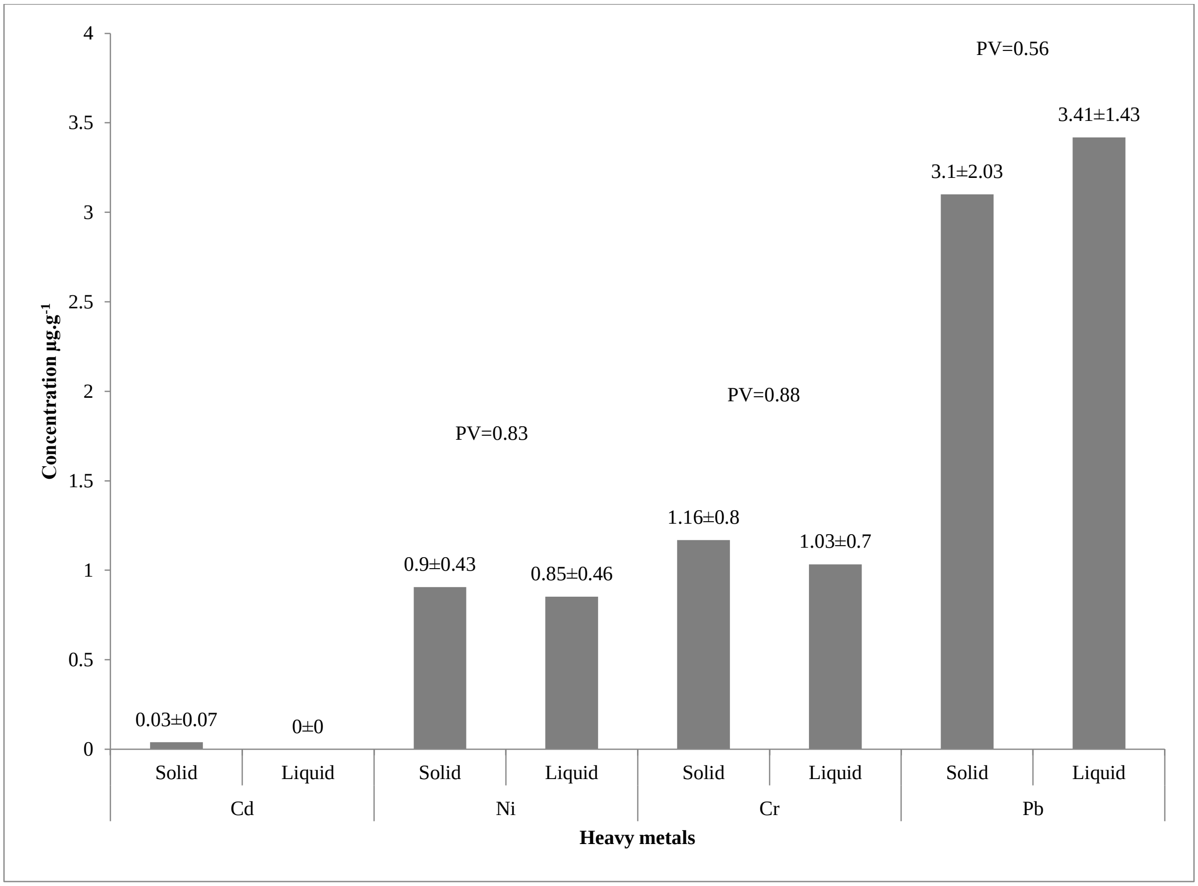

Figure 1. Mean and standard deviation of heavy metals concentrations in highly-consumed lipsticks in Kashan, Iran (µg g^{-1}).

According to the obtained results, the average concentrations of metals in liquid and solid lipsticks were lower than the maximum admissible limits of USFDA regulations for color additives in cosmetics (Table 1). The average concentrations of Pb, Cd, Cr, and Ni in the 16 used codes of lipstick brands can be seen in Table 2. The average concentrations of Pb, Cr, and Ni were statistically meaningful in the codes of liquid (P_{value}<0.001) and solid lipstick brands (P_{value}<0.05). Table 3 illustrates the average concentrations of Pb, Cd, Cr, and Ni in various liquid and solid lipstick colors. The results showed that average concentrations of Pb, Cr, and Ni were statistically meaningful in various liquid and solid lipstick colors (P_{value}<0.05). Also, the results of binary comparisons showed that there were significant differences between all liquid and solid lipstick colors in terms of the average concentration of Pb, but there were no significant differences between light red colors with light orange in liquid lipsticks, dark red colors with light red as well as light orange colors with dark red and light red in solid lipsticks.

Table 1. Levels of heavy metals in lipstick in some other parts of the world.

Lipstick Type of	Country	Pb	Cd	Cr	Ni	References
Lipstick	Brazil, China & USA	*ND-11.7 Mg kg^{-1}	ND-0.022 mg kg^{-1}	ND-12.2 mg kg^{-1}	ND-3 mg kg^{-1}	[9]
Lipstick & lip gloss	Europe, USA, Japan, Canada & Unknown	0.04-3.75 mg kg^{-1}	-	-	-	[10]
Lipstick	Iran	0.05-5.20 μg g^{-1}	4.08-60.20 μg g^{-1}	-	-	[11]
Lipstick & lip balm	China	0.021-2.012 μg g^{-1}	0.0004 –1.201 μg g^{-1}	0.037–7.199 μg g^{-1}	ND-3.667 μg g^{-1}	[12]
Lipstick & lip gloss	California	<0.025-1.32 ppm	<0.002 -3.48 ppm	<0.005- 9.72 ppm	<0.012- 9.73 ppm	[13]
Lipstick	Pakistan	0.28-6.23 ppm	0.2-0.5 ppm	0.22-5.43 ppm	0.6-5.94 ppm	[14]
Lipstick	Italy, France, Canada UK, USA and Korea	0.3-2.44 ppm	0.004-0.02 ppm	16.54-0.17 ppm	0.09-4.24 ppm	[15]
-	** USFDA maximum admissible limits of heavy metals	20 ppm	15 ppm	170 ppm	170 ppm	[35,36]

* ND; Not detectable or <LOD Limit of Detection.
** The US Food and Drug Administration has not determined the level of lead in cosmetics. But the colorants were main source of metals. The USFDA (US Food and Drug Administration) limit for lead as color additive in cosmetics is 20 ppm. For Cadmium is 3 ppm and for nickel and chromium are 170 ppm.

Table 2. Average concentration of heavy metals in 16 lipstick codes

Type of lipstick	Code	Country	Color	Concentration of heavy metal (mean ± SD μg.g^{-1})			
				Pb	**Cr**	**Ni**	**Cd**
Liquid	**4**	**1**	**Dark red**	2.42 ± (0.11)	0.82 ± (0.07)	0.70 ± (0.04)	ND*
	6	**2**	**Dark red**	3.93 ± (0.05)	2.12 ± (0.16)	1.70 ± (0.12)	ND
	7	**1**	**Light red**	2.02 ± (0.02)	1.49 ± (0.17)	0.33 ± (0.03)	ND
	8	**2**	**Light orange**	2.03 ± (0.06)	ND	0.59 ± (0.03)	ND
	10	**3**	**Light pink**	5.83 ± (0.07)	1.17 ± (0.12)	1.12 ± (0.09)	ND
	11	**4**	**Dark orange**	4.25 ± (0.30)	0.58 ± (0.02)	0.65 ± (0.09)	ND
P value				0.001	0.001	0.001	-
Solid	**1**	**1**	**Light orange**	2.83 ± (0.10)	1.46 ± (1.01)	1.67 ± (0.17)	ND
	2	**2**	**Dark red**	2.25 ± (0.21)	0.93 ± (0.03)	0.62 ± (0.05)	ND
	3	**3**	**Dark orange**	1.83 ± (0.02)	0.45 ± (0.05)	0.62 ± (0.09)	ND

5	**5**	**Light red**	4.54 ± (0.26)	1.15 ± (0.15)	0.60 ± (0.00)	ND
9	**2**	**Light pink**	0.15 ± (0.00)	0.72 ± (0.06)	0.60 ± (0.17)	ND
12	**2**	**Dark orange**	0.03 ± (0.05)	0.64 ± (0.04)	0.54 ± (0.08)	0.19 ± (0.04)
13	**2**	**Light red**	3.92 ± (0.07)	0.56 ± (0.08)	0.60 ± (0.00)	ND
14	**6**	**Dark red**	5.60 ± (0.18)	0.74 ± (0.07)	1.16 ± (0.29)	0.09 ± (0.08)
15	**7**	**Brown**	6.25 ± (0.17)	2.44 ± (0.40)	1.33 ± (0.38)	ND
16	**8**	**Dark orange**	3.57 ± (0.12)	2.56 ± (0.29)	1.30 ± (0.05)	0.10 ± (0.01)
P value			0.001	0.001	0.001	0.001

*ND; Not detectable

Table 3. Average concentration of heavy metals in 16 lipstick codes based on color

Type of lipstick	**Heavy metal**	**Concentration of Heavy metal (mean ± SD μg.g^{-1})**						**P-value**
		Light orange	**Dark orange**	**Dark red**	**Light red**	**Light pink**	**Brown**	
Liquid	**Pb**	2.03±0.06	4.25±0.3	3.17±0.83	2.02±0.02	5.83±0.07	-	<0.001
	Cd	-	-	-	-	-	-	-
	Ni	0.59±0.03	0.65±0.09	1.2±0.55	0.33±0.03	1.12±0.09	-	<0.001
	Cr	-	0.58±0.02	1.42±0.72	1.49±0.17	1.17±0.12	-	<0.001
Solid	**Pb**	2.83±0.1	1.81±1.53	3.92±1.84	4.23±0.38	0.15±0	6.25±0.17	<0.001
	Cd	-	0.15±0.05	0.09±0.8	-	-	-	<0.23
	Ni	1.67±0.17	0.82±0.36	0.89±0.35	* 0.6±0	0.6±0.17	1.33±0.38	<0.001
	Cr	1.46±1.01	1.21±1.02	0.83±0.11	0.85±0.33	0.72±0.06	2.44±0.4	<0.005

* The value is very low and is less than 0.0001.

Also, there were significant differences between dark orange colors and light red and dark red in liquid lipsticks as well as brown colors and light red, dark orange, dark red and light pink in solid lipsticks in terms of the average concentrations of Cr used, but there was no significant difference between other liquid and solid lipstick colors. Binary comparisons for Ni showed that there was no significant difference between light red colors and light orange, dark orange and light red and light orange, light pink and dark red, light orange and dark orange in liquid lipsticks and dark red colors and light red, dark orange and light red, dark red and light pink, light pink and light red and dark red, brown and light orange in solid lipstick, but there was statistically a significant difference between other solid and liquid lipstick colors. Table 4 shows the average concentrations of Pb, Cd, Cr, and Ni in liquid and solid lipsticks of different countries. There was statistically a meaningful difference between different codes of countries in terms of the average concentrations of Pb, Cr, and Ni in liquid and solid lipsticks (P_{value}<0.05).

Table 4. Average concentration of heavy metals in 16 lipstick codes based on Country

Type of lipstick	Heavy metal	Concentration of heavy metal (mean ± SD μg g^{-1})								P value
		1	2	3	4	5	6	7	8	
Liquid	**Pb**	2.22±0.22	2.98±1.04	5.83±0.07	4.25±0.3	-	-	-	-	<0.001
	Cd	-	-	-	-	-	-	-	-	-
	Ni	0.52±0.2	1.14±0.61	1.12±0.09	0.65±0.09	-	-	-	-	<0.001
	Cr	1.15±0.39	2.12±0.16	1.17±0.12	0.58±0.02	-	-	-	-	<0.001
Solid	**Pb**	2.83±0.1	1.58±1.68	1.83±0.02	-	4.54±0.26	5.6±0.18	6.25±0.17	3.57±0.12	<0.001
	Cd	-	0.19±0.04	-	-	-	0.09±0.08	-	0.1±0.01	<0.001
	Ni	1.67±0.17	0.59±0.08	0.62±0.09	-	0.6±0	1.16±0.29	1.33±0.38	1.3±0.05	<0.001
	Cr	1.46±1.01	0.71±0.15	0.45±0.05	-	1.15±0.15	0.74±0.07	2.44±0.4	2.56±0.29	<0.001

Table 5 shows the results from the carcinogenic and non-carcinogenic risk assessment of lipsticks in terms of the average concentration of each metal. According to the results, the highest and lowest levels of SED were found for Cr and Pb metals, respectively. However, for all metals, the levels of SED were less than RFD. The MoS values of all metals were higher than 100, indicating the impossibility of non-carcinogenic risk creation for consumers. Thus, according to the following results, the HQ of non-carcinogenic risk for each metal was also less than 1, and therefore, there is no threat to consumers in the concentrations of the metals in the lipsticks. Finally, according to the HI value of chronic non-carcinogenic risk, which was lower than 1, the possibility of non-carcinogenic risk in total metals is also negligible. The results of this study showed that the MoE values for all metals were higher than 10^4 and therefore, the possibility of carcinogenic risk of these metals in lipsticks is negligible. Also, the possibility of LCR in consumers indicates a very low consumption risk of these metals due to the use of lipsticks during the lifetime. The results of sensitization risk for Ni in the highly-consumed lipsticks in Kashan are shown in Table 5. The findings showed that the CEL of the lipsticks was about 0.0213 μg.cm$^{2\ -1}$.d^{-1} and the AEL for Ni in cosmetic products was 1.4 μg.cm$^{2\ -1}$. As seen, the acceptable level is higher than the exposure level, indicating the absence of potential skin sensitization by these materials.

Table 5. Results of carcinogenic and non-carcinogenic risk assessment of lipstick based on average concentrations

Heavy metal	Mean concentration (μg.g^{-1})	No cancer risk				Cancer risk		Dermal Sensitivity
		SED mg kg bw^{-1}.day^{-1}	MoS	HQ	HI	MoE	LCR	AEL/ CEL
Pb	3.21±1.82	0.025×10^{-6}	160×10^{5}	6.25×10^{-6}	5.11×10^{-3}	0.0252×10^{6}	2.14×10^{-10}	-
Cd	0.024±0.058	1.87×10^{-6}	0.53×10^{5}	1.87×10^{-3}		0.358×10^{6}	12.5×10^{-6}	-
Cr	1.11±0.75	8.67×10^{-6}	0.34×10^{5}	2.89×10^{-3}		0.016×10^{6}	4.33×10^{-6}	-
Ni	0.88±0.43	6.88×10^{-6}	0.29×10^{6}	3.44×10^{-4}		0.04×10^{6}	6.26×10^{-6}	>1

DISCUSSION

In the present study, heavy metals including Pb, Cd, Cr, and Ni in 16 lipstick brands were investigated in Kashan, Iran. According to the results, there was no statistically meaningful difference between liquid and solid lipsticks in terms of the average concentration of Pb. The concentrations of Pb were in the ranges of 0.03-6.25 μg g^{-1} in solid brands and 2.02-5.83 μg.g^{-1} in liquid brands, which were less than the maximum admissible limits of USFDA regulations (Table 1). In a previous survey on 108 lipstick samples, the average concentration of Pb in liquid samples was reported as 3.33 μg g^{-1}. The concentration of Pb in dark lipsticks was also found out to be higher than that in light samples [37]. These amounts are consistent with the average concentration of Pb in the present study. Moreover, in the present study, brown color contains the Pb in a higher amount than any other colors do. Another study on 35 samples of highly-consumed lipsticks in Isfahan's markets, detected that the range of Pb concentration was 0.08-5.2 μg.g^{-1} and lipsticks in copper and pink colors were observed the highest (2.21 μg g^{-1}) and lowest (1.37 μg g^{-1}) average concentration of Pb [11]. These concentration ranges were lower than the Pb results of the present study. In this research, brown color comprised the higher amount of Pb (6.25 μg g^{-1}), and dark orange color had a lower amount of Pb (0.03 μg g^{-1}).

In all solid brands, the concentrations of Cd (range from not detectable (ND) to 0.19 μg g^{-1}) were lower than the maximum admissible limits of USFDA regulations. In some studies, the tested lipstick and lip gloss products carried the maximum amount of Cd to 4 μg.g^{-1} which was not remarkable [2, 13, 15, 38]. A previous study reported the high concentrations of Cd (5- 10 μg g^{-1}) in low-cost non-branded samples from China and India [8]. According to a study by the New Zealand Centre for Public Health Research on lipsticks, the concentrations of Cd were found in the range of 0.1-1 μg g^{-1} in 50 lipstick samples and in the range of 1.1-110 μg g^{-1} in 36 lipstick samples [39]. The comparison of the results of the present study with the abovementioned study indicates that there are high levels of Cd in the consumed lipsticks in New Zealand. A study showed that the concentration range of Cd in lipsticks was between 4.08-60.2 μg g^{-1}, which was higher than the Cd results of the present study. Also, the highest average concentration of Cd (27.2 μg g^{-1}) was found in lipsticks in copper color and its lowest average concentration (13.30 μg.g^{-1}) was found in pink lipsticks [11]. While, in the present study, the mean concentration of Cd was less than 0.2 μg g^{-1} in dark orange and dark red lipsticks.

The average concentrations of Cr in liquid and solid lipsticks were not statistically significant. The concentration of Cr was in the range of 0.45-2.56 μg.g^{-1} in solid brands and of ND-2.12 μg g^{-1} in liquid brands which were less than the maximum admissible limits of USFDA regulations. In all samples of the lipsticks tested in the previous study, the average concentration of Cr was in the range of 0.222-5.430 μg g^{-1}. Also, this study indicated that the dark brown and red colors had the highest and lowest Cr concentrations, respectively [14]. While in the present study, the highest and lowest amounts of Cr were found in dark orange and light orange colors. In a study, the Cr concentration was reported as less than 10 μg g^{-1} in most of the lipstick samples, [40]. Another research demonstrated the Cr concentrations with lower amounts than 1 μg g^{-1} [3]. A previous study reported the Cr level higher than 10 μg g^{-1} [8] and in New Zealand, it was reported in the range of 100-230 μg g^{-1} in a number of lipstick samples [39].

The average concentration of Ni in liquid and solid lipsticks was not statistically meaningful. The Ni concentrations were in the range of 0.54 – 1.67 μg g^{-1} in solid brands and 0.33- 1.7 μg g^{-1} in liquid brands which were less than the maximum admissible limits of USFDA regulations. In the present study, Ni was found in nine of the 16 brands of lipsticks. The maximum and minimum amounts of this metal were found 1.06 μg g^{-1} in the golden lipstick and 0.06 μg g^{-1} in the pink lipstick, respectively [3]. Compared to the obtained results of this study, the highest amount of Ni was 1.7 μg g^{-1} which was found in the dark red lipstick, and the lowest amount of this metal was found 0.33 μg g^{-1} in the light red lipstick. Another work showed that all samples of lipstick had Ni and the maximum and minimum amounts of this metal were 4.2 $\mu g.g^{-1}$ and 0.09 $\mu g.g^{-1}$, respectively [15].

Several studies have reported the presence of different concentrations of heavy metals in a variety of cosmetics by brand, color type, etc. [11, 14, 37]. It seems that even in the best conditions of factory production, heavy metal contamination can be observed. Therefore, to diminish the adverse health effects of heavy metals, cosmetics producers must use such ingredients as color additives in their cosmetics according to FDA's requirements [11].

The heavy metals levels in cosmetics compared with other sources such as soil, water, food, etc. are minimal. But the risk of toxicity of these small amounts should not be ignored for several reasons. These products are used daily for a long time and on the other hand, they are used in sensitive areas on the skin, such as around the eyes and lips. The most important concern about these cosmetics was the little knowledge of consumers about the presence of heavy metals in cosmetics [41].

Cutaneous sensitization such as allergic contact dermatitis (ACD) can be a result of using cosmetics, household, and laundry products that contain various chemicals. So, there is a requirement to recognize and determine skin-sensitizing chemicals and to identically distinguish the health risks that may result from exposure [42].

According to our results (Table 5), the non-carcinogenic risk indicator (HI) for Pb, Cd, Cr, and Ni were lower than 1 and it is placed within safe limits. A previous study reported that the dose of daily systematic exposure and safety margin of Pb in lipsticks from south of Nigeria were 1.32×10^{-6} mg.kg $bw^{-1}.day^{-1}$ and 3.02×10^{6} [43], respectively, which were high compared to our results. Also, the results of the carcinogenic risk assessment of heavy metals in this study showed that the indicator of MoE was higher than 10^4 and the LCR was lower than 10-6, indicating the low probability of carcinogenic risk. A similar study demonstrated that the MoE and LCR values for Pb, Cd, Ni, and Cr in cosmetic products consumed in Korea were 1.73×10^4, 8.82×10^9, 3.53×10^7, and 1.25×10^5 as well as 3.09×10^{-10}, 1.14×10^{-9}, 7.21×10^{-9}, and 5.59×10^{-7}, respectively. Also, they showed that there wasn't any risk of dermal sensitization due to the exposure to these products [26], which is consistent with our results.

A previous study reported that the main exposure metric for the increase of cutaneous sensitization is the dose of chemical per unit region of skin and this is related to the exposure metric for the risk assessment of contact allergens [42]. Another study demonstrated that the AEL/CEL ratios of 25 fragrance allergens ingredients in 107 perfumes were below 1 and the utilization of these potential skin sensitizers is not considered safe [44]. In contrast, our findings showed that the AEL/CEL ratio of Ni in lipsticks was more than one, which indicates the absence of potential skin sensitization by these materials.

CONCLUSIONS

The results of this study showed that the mean concentrations of Cd, Cr, Ni, and Pb in solid lipsticks and liquid samples were lower than the maximum admissible limits of USFDA standards. For all metals, the levels of systematic exposure dose were less than RFD, and also, the HI of non-carcinogenic risk for all metals was lower than 1. Therefore, these products are no threat to consumers in the concentrations of the metals. The MoE and LCR values were higher than 10^4 and below 10^{-6}, respectively. So the improbability of carcinogenic risk of the abovementioned metals was observed in the consumption of solid and liquid lipsticks. Also, the result of sensitization risk for Ni indicated the absence of potential skin sensitization by these materials.

Regarding the potential effects of the abovementioned metals on human health, some necessary measures should be taken to control the entrance of cosmetic products of poor quality into the country and to draw up a national standard for the permitted volume of heavy metals in the lipsticks produced and distributed throughout the country. It should also include a list of lipstick ingredients attached to the packaging for consumers to select the precise products.

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Conflict of interests

The authors declare that there are no conflicts of interest.

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