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BIOACCUMULATION OF SUBSTANCES FROM USAGE OF CONTAMINATED COSMETICS IN INDIA AND ITS IMPLICATIONS ON HEALTH

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Abstract

This paper focuses on highlighting the consequences of using contaminated cosmetic products. Prolonged exposure to heavy metals and harmful organic substances has been related to significant acute and chronic health implications. The data referred to in this paper is presented in the context of Indian cosmetic regulations as it delves into the gaps in the current cosmetic legislation in India and the scope for improvement. It further reviews the route of exposure and the mechanism of toxicity followed by such compounds. In particular, it sheds light on the carcinogenic substances. It also discusses the alternatives that can be used in cosmetic products and important considerations to keep in mind regarding the use of these alternatives. Nowadays, curbing our exposure to toxic substances must be prioritised, and it is necessary to include cosmetic products in this discussion.

Keywords

Cancer, Cosmetics, Cosmetic Regulations, Exposure, Health implications, Heavy metals, Organic compounds, Toxicity

Introduction

With the rapidly evolving, ever-growing personal care and cosmetic industry of India, there has been an even greater surging public concern regarding the ingredients that are used up to make these cosmetic products. The importance of using safe low-risk ingredients cannot be stressed enough. Cosmetic products are applied daily, in different amounts and for different durations of time. This prolonged exposure to cosmetics calls for safe ingredients to be used to minimise the damage to one's health. However, in this constantly changing industry with a widening number of cosmetic brands, pioneer products, and novel ingredients, it is certainly difficult to keep up.

Since the inception of the original regulation on cosmetics in India, namely Drugs and Cosmetics Act 1940, Drugs and Cosmetics Rules 1945 and Labelling Declarations by Bureau of Indian Standards (BIS) [1], we have witnessed little change in the sphere of cosmetic regulation in India. While these regulations are clear and coherent in their structure and form, aligned in terms of their intended meaning and actual interpretation and logical in its essence and substance, there is a severe lack of implementation and enforcement of these regulations. Oversight and monitoring of the aforementioned regulations remains a herculean task in a country such as India. This boils down to the size of the country, an unorganised cosmetic sector and lack of coordination.

Such a lack of implementation of these regulations has greater implications on health and safety of consumers. Increased exposure to heavy metals and harmful organic substances through cosmetic products has a detrimental impact on the health of the individual. Furthermore, the regulations are not well-crafted simply because they fail to include the broad spectrum of widely available and used ingredients and discuss only a limited number of select ingredients. The lack of prompt renewal or update of the existing regulation has hindered the legalities to keep up with the industry. This inhibits the assessment of safety of such new materials and limits the scope and contours of India's cosmetic regulation.

The most commonly found undesirable substances used in cosmetic formulations are heavy metals. Heavy metals are widely used in cosmetics. There are a number of reasons behind inclusion of heavy metals in cosmetic formulations. Heavy metals are often used as colourants in formulations. They may be included due to a convenience and cost factor. Heavy metals also tend to be included in formulations by chance due to contamination of the ingredients used. Secondly, many harmful organic substances also make their way into cosmetic formulations. These include parabens, phthalates, formaldehyde, and formaldehyde releasers among others. In this paper, the routes of exposure, mechanisms of toxicity and effect on human health, in particular carcinogenesis, of certain substances will be discussed in the context of Indian cosmetic regulations.

Methods

The primary research methodology followed for this paper is literature review. The paper comprises an evaluation of existing literature, comparison and contrast in different data that has been evaluated according to different variables and deepen the understanding of the relation between use of contaminated cosmetics and cancer risk in India.

Data regarding the extent of application of heavy metals and certain harmful organic in cosmetic products in India is available in scientific journals and other online publications. After understanding the context and status quo of regulations, legal constructs, and limits and ppm range approved by the government, the data published has been used to determine the extent of adulteration in cosmetics in India and further understand the correlation between use of contaminated cosmetics and cancer. This paper would also analyse the route of exposure to heavy metals or harmful organic substances, their mechanism of toxicity and implications on human health. This provides the necessary context to fully understand the need for further research in this area.

The route of exposure to heavy metals

Each cosmetic formulation is created with a specific purpose. The ingredients are chosen in alignment with the purpose and function of the cosmetic and the target area of application. However, often heavy metals also find their way into the formulations, sometimes deliberately (for example, as colouring agents) and sometimes unknowingly (from contaminated sources). The application of cosmetics may pose a threat to the health of the individual using products that contain such ingredients. While there is a certain level of knowledge and awareness regarding the health implications of heavy metals, the issue has not been effectively addressed and heavy metals are used frequently in cosmetic products. This issue requires considerable policy reforms through stringent monitoring and healthcare assistance through preventive and effective treatments.

There may be a number of reasons why heavy metals are present in formulations. First, heavy metals may be used as ingredients. They, thus, may be added intentionally into formulations. Some heavy metals which are commonly used in cosmetic formulations include lead, mercury, arsenic, cadmium, nickel, and chromium. Each of these metals possesses its own qualities and properties on the basis of which its application is decided.

Lead is used as a colour additive in cosmetic products. It is commonly included in eyeshadows and traditional eyeliners (kohl, kajal, surma, and equivalent), blushes, lip products, shampoos, body lotions, and hair dyes. [2] It is also used in Sindoor. [3] Mercury is used as a whitening agent, for fading freckles and spots as well as treatment of acne. It is commonly included in creams and lotions. Phenyl Mercuric salts are commonly used as preservatives in eye makeup and eye makeup removal products. Arsenic is used as a colour additive, with applications similar to lead. It is found in Sindoor, traditional eye cosmetics and eye shadow, hair dyes, skin foundation and lightening creams, and lip products. [4] Nickel is found in lip products including lipsticks, lip gloss, and lip balms. Additionally, nickel is present in eye shadows, hair dyes, mascaras, and shampoos. [4] [5] Hexavalent chromium is an impurity that contaminates cosmetic products at the manufacturing stage. It is also used as a colour additive and is generally found in lip products. [6] Cadmium is used in lipsticks, eye shadows, and face whitening creams and powders. [7]

Second, heavy metals may find their way into formulations unintentionally as impurities. Ingredients may be contaminated during the manufacturing or due to improper extraction, processing, and refining. Poor QA/QC and purification of chemicals can be an indicator of such issues.

Heavy metal exposure through cosmetics proceeds through dermal or topical application. Upon entry into the body, the heavy metal may cause topical or systemic health effects. At the point of application of the product, accumulation of the heavy metal at the site's stratum corneum may produce local effects. These effects may manifest in the form of allergic contact dermatitis due to excess of the metal as it binds with keratin. Upon repeated application of contaminated cosmetics, heavy metals tend to accumulate at those sites and act as reservoirs of the metal. This causes a long-term exposure to the metal, even if the cosmetic is no longer used. Such long-term exposure may cause systemic issues. Certain heavy metals including Cd, Pb, and Hg, may penetrate through the skin layers, enter general circulation and transport to different organs while other metals like Ni only reach the general circulation. The metals permeate the skin through sweat glands and hair follicles. Facial skin, being thinner, is more permeable than skin anywhere else on the body. Furthermore, cosmetic products applied to the lips or within the buccal cavity (for example toothpastes and mouthwashes) may be orally ingested. Hand to mouth transfer of cosmetics after application using hands is also possible. Cosmetics which contain moisturising agents when applied to the skin increase the permeation of the skin. This allows the entry of heavy metals and the xenobiotics they may be bound with. Thus, the xenobiotics also find their way into general circulation. Besides binding with exogenous substances, heavy metals may also replace the beneficial metals which are bound to endogenous biological molecules. These molecules include thiol, amine, and carboxylic functional groups found in structural proteins (for instance keratin, collagen, myosin, and actin) and functional proteins (for instance enzymes). These molecules also include nucleic acids. Bonding of heavy metals with nucleic acids may result in damaged DNA and RNA which may lead to carcinogenesis. [4]

Heavy metal mechanism of toxicity

Toxicity of any substance cannot be considered a direct measurable parameter as toxicity is further dependent on a number of factors. These include dose (this refers to the dose per application), form of metal/type of compound, nature of biological object being affected (for instance the age of person exposed; this will help us understand the correlation of susceptibility of getting cancer due to use of contaminated cosmetics and age of person exposed and helps us identify if the vulnerable populations (children and elderly) are more at risk), duration of exposure (this refers to the average per application duration of exposure), frequency of application (this factor relates to how often the product is applied), and route of exposure. [8]

The human Skin Barrier, Lipid Barrier, or Moisture Barrier, found in the stratum corneum of the epidermis, constitutes a layer of lipids, fatty acids, and ceramides produced by keratinocytes along with corneocytes, which is a layer of dead cells. [9] Heavy metals possess the ability to induce lipid peroxidation in this Skin Barrier. Heavy metals readily produce free radicals that attack polyunsaturated fatty acid residues of phospholipids, producing lipid peroxides. Upon subsequent reactions with redox metals, producing mutagenic and carcinogenic biomarkers including malondialdehyde, 4-hydroxynonenal and other exocyclic DNA adducts. [10]

Exposure to heavy metals may lead to the manifestation of a variety of health concerns. Acute and chronic poisoning may be a consequence of exposure to heavy metals through inhalation, ingestion and dermal routes. Each heavy metal has its own short-term and long-term implications on health. Bioaccumulation of heavy metals due to prolonged exposure to these heavy metals leads to toxic effects on our body systems. Different heavy metal salts and oxides follow similar mechanisms of action and have similar pathways of inducing toxicity through ROS generation and limiting antioxidant action or bonding with sulfhydryl and other functional groups.

Once the heavy metals have entered the body via any of the routes of exposure, they bind to enzymes, proteins, lipids and proteins through –SH groups or thiol/sulfhydryl groups. This process modifies the cysteine residues in protein and causes protein inactivation. This may lead to subsequent disruption in the intracellular redox state imbalance in the antioxidant defence. Figure 1 shows the bonding of a Cd ion with the sulfhydryl group in a protein as an example. [11] [12]

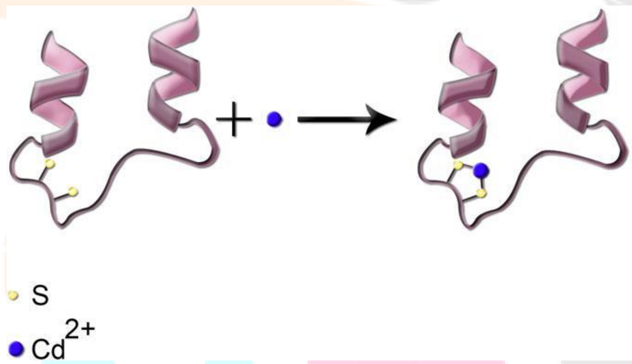


Figure 1: Bonding of a Cd ion with the sulfhydryl group in a protein [11]

Heavy metals are capable of producing free radicals, primarily ROS and RNS generation. ROS includes hydroxyl radicals, peroxides, superoxides, single oxygen atoms and alpha oxygen particles. ROS and RNS can induce oxidative stress. Oxidative stress initiates a chain reaction in the body where free radicals attract electrons from neighbouring cells, thereby destroying balanced cells and creating more free radicals, ultimately leading to cellular damage. ROS generation affects macromolecules, induces oxidative stress, and depletes antioxidants. It creates an imbalance between oxidants and antioxidants in the body that can lead to drastic internal damage. Table 1 below details the effect of a few heavy metals on ROS generation and consequent results. [11] [12]

METAL	EFFECT ON ROS GENERATION
Ar	Arsenic is known to produce superoxide (O_2^{-} .), oxygen (O2.), nitric oxide (NO.), hydrogen peroxide (H2O2), and peroxyl (ROO.) radicals.
Pb	Lead significantly affects the antioxidant and oxidant parameters. It depletes antioxidant parameters including GPx, CAT, SOD, GST, and GSH and increases oxidative parameters such as MDA and H2O2. Pb induces toxicity: 1. Directly through ROS production. 2. Indirectly by depleting cellular antioxidants.

Cr (VI)	ROS and RNS generation induced by Chromium (VI) depletes antioxidant power at cellular level. This leads to oxidative stress and the toxicity of DNA, lipids and proteins.
Cd	Cadmium may lead to oxidative stress in the following manner: 1. Indirectly generating ROS such as O_2^{-} ., hydroxyl (OH), and NO radicals. This increases the pressure on the cellular antioxidant defence. It generates ROS indirectly through the replacement of iron and copper in cellular proteins with Cadmium. The excess iron and copper builds up the oxidative stress. This replacement of important minerals disrupts cellular metabolism. 2. Depleting glutathione.
Hg	Mercury, through increased ROS generation, affects the CNS and cardiovascular system. It leads to reduced activity of antioxidant enzymes including glutathione peroxidase, catalase, and SOD. Alternatively, mercury also has a high affinity for -SH groups and this too leads to decreased activity of glutathione peroxidase. This interferes with intracellular signalling of receptors. Hg induces toxicity: 3. Directly through ROS production. 4. Indirectly by depleting cellular antioxidants. Methylmercury (Me-Hg) in particular leads to activation of phospholipase D (PLD). Increased PLD activation has been linked to many cancers and diseases in humans.

Table 1 [11] [12]: Different heavy metals and their effect on ROS Generation

Figure 2 and Figure 3 describe the route of exposure to heavy metals and the mechanism of toxicity in a concise manner.

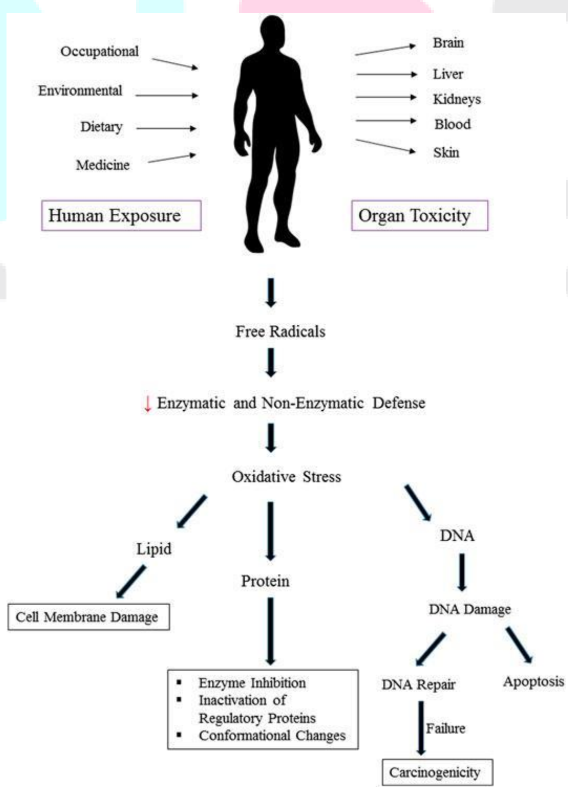


Figure 2: The route of exposure to heavy metals and the mechanism of toxicity [11]

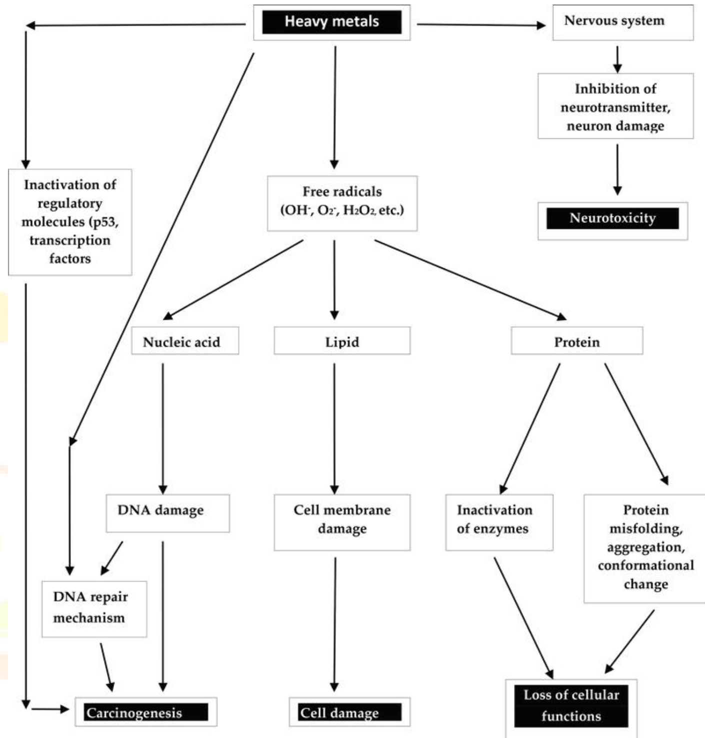


Figure 3: The route of exposure to heavy metals and the mechanism of toxicity [12]

Health implications of heavy metal toxicity

Heavy metals disrupt basic cellular functioning. They impact cellular growth, proliferation, differentiation, damage-repairing processes, and apoptosis. However, this oxidative stress can cause greater problems than just cellular damage. Prolonged cellular damage chain reaction can lead to cell necrosis. ROS creates disturbances in cell signalling pathways for proteins and causes DNA and RNA damage by disrupting the enzyme functioning. DNA damage and defects in DNA repair due to induction of oxidative stress has also been linked to the carcinogenicity of certain heavy metals such as chromium, cadmium, and arsenic. Excessive ROS and subsequent oxidative stress give way to respiratory issues and several diseases including cancer. This also leads to ageing. ROS generation disrupts and inhibits metabolic pathways and causes metabolic abnormalities, altered hormones, and organ and immune system dysfunctions. [11] [12]

Heavy metals can lead to a number of health implications. For instance, many heavy metals are linked to carcinogenesis. Heavy metals may induce carcinogenic effects through proteins or transcription factors.

Heavy metals may induce carcinogenic effects by targeting and bonding with regulatory proteins. These proteins may be signalling proteins or cellular regulatory proteins which participate in cellular functions including differentiation, apoptosis, DNA repair or methylation, cell cycle regulation or simple cellular growth. [11] [12]

Redox-sensitive transcription factors control expression and characterisation of genes responsible for inducing apoptosis, controlling the proliferation and growth of damaged cells, repairing any damaged DNA and strengthening the immune system. These transcription factors include AP-1 or Activator protein, NF-κB or Nuclear Factor-kappa B and p53. The carcinogenic effects induced by heavy metals that are related to the activation of these transcription factors are realised through the repeated cycling of electrons by the antioxidant network. The free radicals produced by heavy metals inside cells selectively activate the transcription factors and consequently lead to cellular death or proliferation. Both AP-1 and NF-κB are involved in the mitogen-activated protein (MAP) kinase pathways. AP-1 is responsible for cell growth and cellular differentiation while NF-κB controls inflammatory responses. Both the transcription factors are involved in cell proliferation, apoptosis, and regulation of p53. Metal signalisation of these transcription factors is realised in the MAP kinase pathways. The p53 protein is involved in controlling cell division and cell death. Inactivation or mutations of p53 causes uncontrolled cell division, which has been linked to cancer. A mutated p53 loses its ability to control cell division and leads to the growth and spreading of cancer cells. [11] [12]

The expression of genes is affected, causing uncontrolled cell division and cell growth. Heavy metal exposure has been related to Ras protein mutations. For instance, As exposure has been related to overexpression of Ras protein in prostate epithelial cells in humans. Similarly, Cd may cause a spike in the levels of ERK ½ and the transcription factors jun and fos, as observed in vitro. Cr (VI) may also cause overexpression of jun, as observed in cultured cells. These results have significant implications. A mutated Ras protein is permanently activated, the gene is permanently turned on, and the kinase cascade cannot be stopped. Overexpression of jun and fos or the intensified activation of ERK ½ also repeatedly carries on the gene expression. Such factors lead to a permanently activated signalling pathway which causes proliferation, ultimately causing increased tumour growth. [11] [12]

Heavy Metal	**About the metal**	**Acute Exposure effects**	**Chronic Exposure effects**	**Treatment**
Mercury	Mercury is a neurotoxin. Mercury is readily absorbed through the skin upon topical exposure. It also has a tendency to accumulate in the body. [13]	1. Skin Irritation 2. Allergic reactions [13]	1. Inflammation in liver, kidneys and urinary tract. 2. Neurotoxic manifestations including hearing, speech and motor difficulties, insomnia, memory loss, tremors, anxiety and depression. 3. In-utero exposure leads to developmental issues in children including motor difficulties, sensory problems and mental retardation. [13]	1. Chelation therapy, which comprises the use of chelating agents (type of drugs) to remove the metal from the organs of the body. 2. Treatment of the issues that manifest as a result of mercury exposure. [14]

Arsenic	Arsenic is a carcinogen. Arsenic accumulates in hair, nails and skin. Arsenic absorption via the dermal route is comparatively lower than other routes. [15]	1. Vomiting. 2. Diarrhoea. 3. Hypertension. 4. Muscle cramps. 5. Stomach pain. [16]	1. Dermatitis. 2. Hyper-pigmentation. 3. Keratosis. 4. Increased risk of leukaemia, kidney cancer, and bladder cancer. 5. Damage to the nervous system. 6. Liver enlargement. [15]	1. Chelation therapy. 2. Supplements in diet, potassium in particular can decrease severity of heart related issues. 3. Treatment of the issues that manifest as a result of arsenic exposure. [16]
Nickel	Nickel ion release is aggravated by preservatives, acids, sweat and high temperatures.	1. Allergic reactions. [15]	1. Affect kidneys, stomach and liver. 2. Lung fibrosis. 3. Cardiovascular diseases. 4. Cancer. [15]	1. Chelation therapy. 2. Phototherapy. [17]
Cadmium	It is a human carcinogen.	1. High blood pressure, hypertension. [18]	1. Irritant dermatitis. 2. Kidney and liver Damage. 3. Respiratory issues including bronchitis, pulmonary oedema, chemical pneumonitis. 4. Damage to the nervous system (peripheral neuropathy, muscle weakening, numbness, and tingling). 5. Low bone mineral density. 6. Endocrine disruptor. Hampers with hormonal systems. [15]	1. Gastrointestinal tract irrigation. 2. Chelation therapy. 3. Plasma exchange. [18]

Lead	Lead body burden lies in the bones in human bodies. Bones then release this lead increasingly during bone turnover periods. Lead has a half-life of more than 20 years. [19]	1. Fatigue 2. Vomiting 3. Headaches 4. Hyperactivity [19]	1. Disrupt the oxidant-antioxidant system of the body. 2. Inflammation in organs. 3. Lead affects the reproductive system of the body. It can cross the placenta during pregnancy and can lead to foetal death, premature deliveries and low body weight of the baby at the time of birth. It also leads to developmental issues in the child. 4. Anaemia in children. 5. Hypertension. 6. Effect on hematopoietic system. [19]	1. Chelation therapy and EDTA chelation therapy. 2. Bowel irrigation. 3. Treatment of the issues that manifest as a result of lead exposure. [19]
Chromium	Hexavalent chromium is a carcinogen.	1. Allergic skin reactions. 2. Redness and swelling of skin. [15]	1. Dermatitis. 2. Ulcerations. 3. Anaemia 4. Damage to stomach and intestines. 5. Increased risk of cancer. [15]	1. Chelation therapy. 2. Exchange transfusion to reduce chromium blood levels. 3. Treatment of the issues that manifest as a result of chromium exposure. [20]

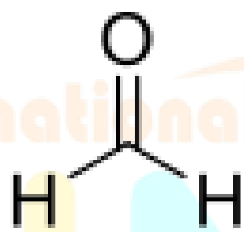
Table 2: Certain heavy metals, their health implications and their treatment

Data on heavy metal contamination of cosmetics in India

A number of studies have been conducted to understand the extent of contamination of cosmetic products in India. In a study conducted by Pollution Monitoring Laboratory, Centre for Science and Environment to assess levels of heavy metals sold in India. 50% of the lipsticks sampled were contaminated with chromium. This paper kept in mind the estimated daily dose through estimated duration and quantity of application and found that the estimated intake of chromium through lipsticks fell in the range of 10.8% to 427.9% of ADI in case of average use of 24 mg/day of lipstick and in the range of 39.2% to 1551.2% of ADI in case of high use of 87 mg/day of lipstick. [1] Another study focused on Bangalore, India found the concentration of Nickel (Ni) ranged from 28.2911ppm to 26.713ppm in lipstick samples and 31.383ppm to 27.670ppm in whitening cream. While this paper is specific to Bangalore, the data can be used in a study with a broader scope, considering the brands that have been sampled are widely available throughout India. These studies provide an insight into the status quo of heavy metal contamination of cosmetic products. Such contamination has great implications on one's health, as discussed. [21]

Mechanism of toxicity of certain organic compounds and its implications on human health

There have been discussions on the toxicity of certain organic compounds used in personal care products. Prime examples of harmful organic substances commonly found in cosmetic products include formaldehyde, phthalates, parabens, long-chain per- and polyfluoroalkyl substances (PFAS) and m- and o-phenylenediamine. Besides the actual substance, there may be other chemicals used in formulations that are associated with the harmful substances. For instance, paraformaldehyde and methylene glycol are types of formaldehyde and quaternium 15 releases formaldehyde. [22] The following table 3 describes key points related to the aforementioned compounds.

Name of substance	Structure	Use in cosmetics	Health effect
Formaldehyde (including types of formaldehydes such as paraformaldehyde and methylene glycol)		Chemical preservatives. Prevent microbial (bacteria/mold) growth "Needed" when formulation is water-based. Used in a range of different cosmetic products. [23]	Known carcinogen. [22]
Phthalates		Used as plasticizer in nail polishes to avoid cracks and make them less brittle. Used in hair sprays to avoid stiffness of hair prevented by a film formed around the hair. Used as a solvent and fixative in fragrances. Used as gelling agents in shampoos. They also help in retaining a fragrance in the formulation. [24]	Dibutyl and diethylhexyl phthalates disrupt functioning of hormones and harm the reproductive system. [22]

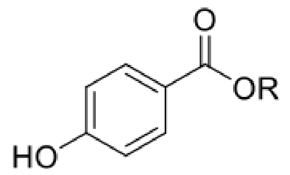
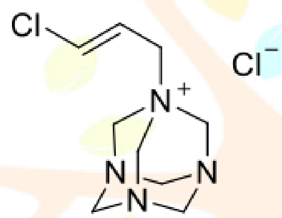
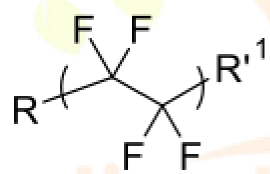
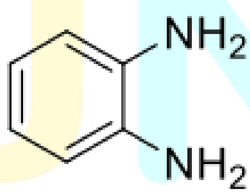
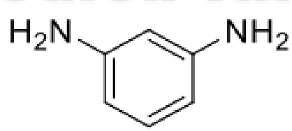
Parabens		Used as preservatives Prevent microbial (bacteria/mold) growth Products containing parabens last longer. Used in a range of different cosmetic products. [25]	Isobutyl and Isopropyl parabens disrupt functioning of hormones and harm the reproductive system. [22]
Quaternium 15		Used as a surfactant and preservative. [26]	Releases formaldehyde. [22]
PFAS		Used to make the skin smooth, conditioned, and shiny. It affects the consistency and texture of the product. [27]	Linked to cancer. [22]
M- and o-phenylenediamine	 O-phenylenediamine  M-phenylenediamine	Used in hair dyes. [28]	Irritates and sensitises the skin. [22]

Table 3: Certain organic compounds, their use in cosmetics and health implications

Formaldehyde is genotoxic and cytotoxic, and its exposure has been linked with human cancer, in particular leukaemia and lung cancer. The mechanism of toxicity followed by formaldehyde involves oxidative stress. The altered gene expressions and mutations may disrupt the hematopoietic system, and consequently cause leukaemia. Formaldehyde induces DNA damage and chromosomal changes. [29]

A number of organic compounds are known endocrine disruptors. Endocrine disruptors cause alterations in the development and functioning of reproductive systems. The first group that comes under endocrine-disruptive chemicals (EDCs) is parabens. Parabens have been increasingly associated as a cause of development of breast cancer. Figure 4 highlights the four pathways parabens may follow to induce carcinogenesis. As highlighted in sections A and B of figure 4, parabens cause DNA damage as they induce target gene expression. In particular, A depicts the estrogenic and antiandrogenic effects of paragen. Parabens (light green circles in the figure) mimic estrogenous hormones and bind to oestrogen receptors (ER) causing subsequent disruptions in the functions of the oestrogen hormone and ERs. In B, the non-genomic activity of parabens is highlighted. Parabens, through the membrane-bound G-protein coupled oestrogen receptor (GPER) induce target gene expression. (TF: Transcription factor). Parabens, through Section C of the image depicts disruptions in the functions of protective enzymes. Parabens inhibit the functioning of aromatase, an enzyme that plays a key role in the biosynthesis of oestrogens. Parabens modulate local oestrogen levels and tamper with the local hormonal balance by inducing aromatase, which converts androgens into oestrogens. They also inhibit 17β-HSD2, which oxidises strong oestrogen into weak oestrogen. Lastly, section D depicts how parabens induce cell proliferation. It shows the crosstalk of parabens with epidermal growth factor receptor 2 (HER2), a transmembrane protein of the epidermal growth factor receptor family. Parabens synergically act with the HER2 ligand (HRG) to induce oncogenic c-Myc expression in the presence of ER activation. (TF: Transcription factor, blue triangle: HER2 ligand, Heregulin or HRG). [30]

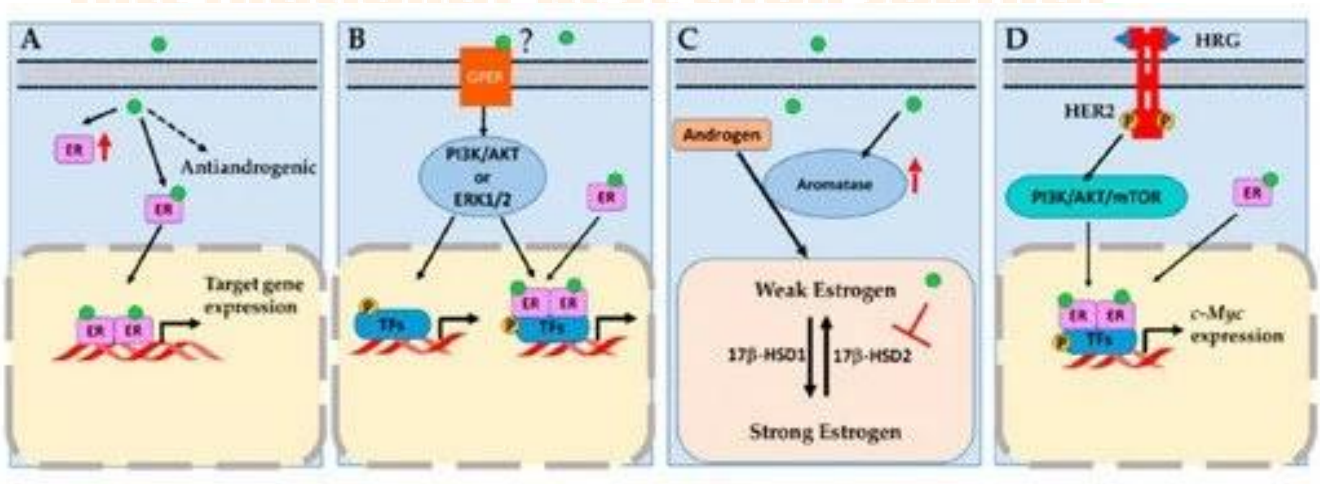


Figure 4: Pathways parabens may follow to induce carcinogenesis [30]

Phthalates are known weak endocrine disruptors and androgen blocking chemicals. Phthalates, along with endocrine disruption, also follow intracellular mechanisms to induce toxicity. Phthalates induce toxicity via affecting the antioxidant enzyme activity and affecting gene expression. Phthalates impact health through mechanisms including oxidative stress due to the generation of ROS, DNA damage, lipid peroxidation, disruption of cell function and affecting the expression and functioning of antioxidant enzymes. [31]

Lastly, PFAS are long-chain flourocarbon compounds found in cosmetics to increase the durability and of the product and to make it water resistant. [32] However, PFAS are highly persistent with a half-life of 3-5 years and can bioaccumulate. PFAS have been associated with disorders in development and reproductive systems due to endocrine and immune dysfunctions. They also may lead to the onset of chronic diseases including thyroidism, obesity, diabetes, and cancer. In India, PFAS have been detected in higher concentrations in females. They have been found in human breast milk, drinking water, ground water, river water, human tissue, and human hair. [33] While there is no established correlation, a higher concentration in women could be due to greater exposure to PFAS. This exposure could be from the use of cosmetics, considering a greater use of cosmetic products among women in comparison to men. [34]

The context and status quo of regulations, legal constructs, and limits and ppm range approved by the Indian government.

"Any article intended to be rubbed, poured, sprinkled or sprayed on, or introduced into, or otherwise applied to, the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance, and includes any article intended for use as a component of cosmetic." [35]

This very definition of a cosmetic under the Drugs and Cosmetics Act 1940 Section 3 [aaa] underscores the necessity of having a regulated cosmetic industry. Considering how cosmetics primarily involve the application of the product on the skin, it is crucial to note that this provides a dermal route to exposure to the ingredients used in the product. Application of cosmetics is not a one-time action; a number of cosmetic products are applied daily for a long duration. The frequency of application, duration of application and number and quantity of products applied give the ingredients ample time to be absorbed via the dermal route. Prolonged exposure to any harmful substance can have detrimental impact on the health of the individual. A well-defined and functional regulatory system is essential to ensure use of safe ingredients and a correct proclamation of the list of ingredients by manufacturers. It guarantees utmost safety and quality of products and effective information dissemination from the manufacturers regarding the details of the products.

The cosmetic industry in India is regulated primarily under Drugs and Cosmetics Act 1940 and Rules 1945 with the main administrator of Cosmetic Legislation being the legislative body Central Drugs Standards Control Organisation (CDSCO), under the Drugs Controller General of India (DCGI). The cosmetic regulation follows a decentralised approach and is jointly overseen by CDSCO and State Drug Control Organisations. [36]

Raw material and ingredient control is addressed under BIS 4707 (Part 1 and Part 2): Classification of Raw Materials and Adjuncts released by The Bureau of Indian Standards. These two Indian Standards as published by the Cosmetics Sectional Committee provide classifications of raw materials to establish a standard of quality for all products manufactured or imported. The Committee broadly categorises the ingredients as either generally recognised as safe (GRAS) or generally not recognized as safe (GNRAS) for use in cosmetics. [37]

Schedule Q of the Drugs and Cosmetics Act under BIS 4707 (Part 1): 2020 tackles colourants, dyes and pigments. A GRAS ingredient list has been prepared with specifications regarding the field of applications in which a colourant may be used in cosmetics. It contains 4 broad categories of fields of application:

a) Colouring agents allowed in all cosmetic products.
b) Colouring agents allowed in all cosmetic products except those intended to be applied in the vicinity of the eyes, in particular eye make-up and eye make-up remover.
c) Colouring agents allowed exclusively in cosmetic products intended not to come into contact with the mucous membranes.
d) Colouring agents allowed exclusively in cosmetic products intended to come into contact only briefly with the skin.

Other limitations and requirements specific for each substance are also stipulated, if any. [38]

Under The Drugs and Cosmetics Act,

1. Rule 135 prohibits the import of cosmetics that contain lead and arsenic compounds for the purpose of colouring cosmetics.
2. Rule 135A, similarly, prohibits the import of cosmetics that contain lead and arsenic compounds for the purpose of colouring cosmetics.
3. Rule 145 stipulates that no cosmetic product manufactured should contain lead or arsenic compounds for the purpose of colouring cosmetics.
4. Rule 145D, similarly, stipulates that no cosmetic product manufactured should contain mercury compounds for the purpose of colouring cosmetics.

Additionally, Rule 134 and 144 discuss the restrictions on heavy metal content in permitted Synthetic Organic Colours and Natural Organic Colours used in imported and locally manufactured Cosmetics respectively. [35]

The permitted Synthetic Organic Colours and Natural Organic Colours used in the Cosmetic shall not contain more than:

(i) 2 parts per million of arsenic calculated as arsenic trioxide.

(ii) 20 parts per million of lead calculated as lead.

(iii) 100 parts per million of heavy metals other than lead calculated as the total of the respective metals. [35]

Schedule S of the Drugs and Cosmetics Act under BIS 4707 (Part 2): 2017 provides a list of ingredients other than dyes, pigments and colourants generally not recognised as safe for use in cosmetics (GNRAS list). It consists of 4 categories:

a) Annex A- List of substances which must not form part of the composition of cosmetic products.
b) Annex B- List of substances which cosmetic products must not contain except subject to the restrictions and conditions laid down.
c) Annex C- List of preservatives which cosmetic products may contain.
d) Annex D- List of U.V. filters which cosmetic sunscreen products may contain. [39]

Observations regarding the current cosmetics regulations in India to keep in mind while moving forward

First, it is important to note here the lack of regulation on the packaging used for cosmetic products. Indian Standards are available for the kind of packaging material permitted for use in drinking water bottles and foodstuffs packaging but not for cosmetic products. [37]

Second, the current regulation only addresses the final formulation of the product but does not address the substances that are used for dispersion of the cosmetic product. For instance, benzene is a commonly used substance in spray sunscreens. It is not a part of the final formulation but is a part of the dispersion mechanism of the aerosol and is used for the product to be dispersed in spray form. Benzene is a known carcinogen but remains unregulated since it is not actually a part of the final formulation and goes unchecked by the authorities. [40]

Third, another aspect that needs to be considered is the use of contaminated sources or contamination of desired substances during the extraction process. This profoundly affects the purity of the cosmetic. Heavy metals are usually not included in the formulation knowingly, besides their use in colourants. As figure 5 shows, heavy metal contamination is evident in different resources in India. Use of these resources, say water from a source contaminated with Cadmium, will have great implications on the purity and safety of the product. Heavy metals are commonly used in processing and refining of desired substances. Improper processing and refining of these ingredients leads to remnant heavy metal contamination, which consequently ends up in the final formulation. [41]

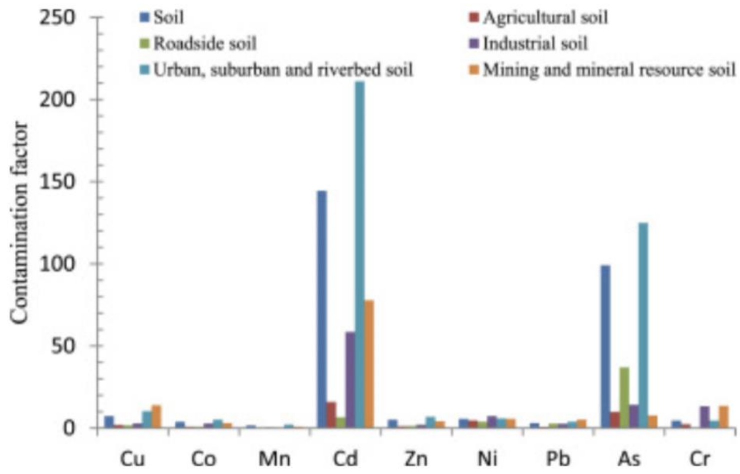


Figure 5: Contamination factor of different heavy metals in urban, agricultural and industrial areas [41]

The cosmetic industry in India is experiencing an unprecedented growth, with a forecast to grow at a CAGR of 16.39% through FY 2026. [42] With a prosperous future of the Indian cosmetic industry in sight, it is necessary for the current regulations to be revamped and updated to embrace the progress of the industry.

The launch of The Cosmetic Rules, 2020 has been a watershed moment in recognising the gaps in the current regulation and building a stronger foundation. The Cosmetic Rules, 2020 come under the Drugs and Cosmetics Act, 1940. Under The Cosmetic Rules, 2020, a concept of a new cosmetic has been introduced which is defined as "cosmetic which contains novel ingredient and has not been used anywhere in the world or is not recognized for use in cosmetics in any National and International literature". Through this concept, the authorities have stepped into regulating the realm of cosmetic products that bring in new technology and new ingredients. This is essential in today's time, where a trend of using never-used-before active ingredients has emerged. The Cosmetic Rules, 2020 has also brought in changes in the application process, registration, and licensing. These processes have been simplified. Additionally, cosmetics manufactured outside India need to comply with The Cosmetic Rules, 2020. A product can no longer be imported in India if its manufacture, distribution, or sale is prohibited in the country of origin. [43] Furthermore, Amendments to The Cosmetic Rules, 2020 have also brought in further changes in the registration and import of cosmetics. [44]

There is a severe lack of implementation of the cosmetic regulations in India due to the absence of proper mechanisms to monitor manufacturing and sale of cosmetics. This is especially true for the unorganised sector in India where there are minimal checks and repercussions for manufacturing, distributing, and selling harmful cosmetics. Such products cater to the rural population in India. Compelled by traditions, rituals, and customs, it becomes inevitable for some to purchase cosmetics that have cultural significance, even if they are contaminated with unsafe substances. The people are coerced by helplessness into purchasing such harmful products because these cosmetics dominate the rural market and are available at cheap rates. There is a lack of safe alternatives. It is commonplace in rural India to find unregulated products that have not been registered, checked, or approved being sold to the people at low prices.

There is a need for increasing cosmetovigilance in India. The term 'cosmetovigilance' refers to "the process of collection, analysis, and assessment of adverse reactions and events appearing in consumers in order to identify any potential health risk, thus guaranteeing a further strengthened safety for consumers." [45] Cosmetic products manufactured, distributed, and sold by the unorganised sector require significant monitoring. India must follow a decentralised approach for this, that is, the local, regional, and central authorities must avail a coordinated cosmetovigilance approach. The local authorities must carry out surveillance checks in their localities to map out the extent of infiltration of contaminated, unregulated, or unapproved cosmetics in the market. Working closely with each other would assist the authorities in achieving this goal efficiently.

Limitations

Certain limitations are bound to arise considering the broad scope and content of this research. There exist limitations of both the data and the analysis. These must be kept in mind while moving forward. The first limitation of the data is that the data collected from different sources may not be of a consistent population or based on a consistent method of checking the purity of samples. Second, accuracy or credibility of the data itself is a concern. Lastly, the data available in this sphere has limited sampling upon which a significant conclusion is based. Limitations of the analysis include not being able to factor out and account for all variables that may hamper the results of the research and the relevance of the result considering the broad scope (India) and limited sampling.

Discussion

There are certain alternatives available that can be incorporated into the formulation in place of heavy metals and harmful organic substances. These alternatives, which perform the same functions and are much safer in comparison to what is being used at present. Mercury, used for brightening, lightning and whitening and to block melanin production, may be substituted by Kojic acid (fungi derived), Niacinamide (vitamin B3 derived) and Vitamin C. Parabens and formaldehyde or formaldehyde releasers, used as preservatives, may be replaced by other plant-derived aldehydes/acids (obtained from spice/herbal/floral plants). Metals and nanoparticles, which are added to formulations as pigments, may be replaced by plant-derived pigments and synthetic pigments. However, there are some important considerations to keep in mind for each of these alternatives. While replacing parabens and formaldehyde or formaldehyde releasers with other plant-derivatives aldehydes or carboxylic acids (such as sorbic acid or benzoic acid), we must understand the implications of introducing such compounds. Carboxylic acids will decrease the pH of the cosmetic product. Especially since formaldehyde is used in water-based formulations, this substitution calls for appropriate pH consideration and adjustment in the formulation. Similarly, replacing metals and nanoparticles with plant-based or synthetic pigments may bring issues in stability of the product. Such new pigments require sufficient heat, pH, and other physical, chemical and microbiological stability tests to procure information regarding their application in cosmetics. Moreover, even compounds such as Kojic acid are not free from health side effects. It inhibits the catecholase activity of tyrosinase. [46] Furthermore, cost and scalability must also be considered for every alternative to effectively map the impact it would have on the product.

Conclusion

It can be effectively concluded that there are strong health implications of prolonged use of cosmetic products containing heavy metals and certain organic compounds. The effect may range from a short-term impact to a chronic impact. There is indeed a correlation between carcinogenesis and some of these compounds. Each compound follows its own mechanism to cause cancer. Furthermore, it is evident that the limitations in the current Indian cosmetic regulation must be covered to bring about a change in the status quo.

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