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LETTER TO THE EDITOR

The Global "Paraben Toxicity" Discourse: A Call for Indian Doctors and Researchers to Step in

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Parabens (*methylparaben, ethyl paraben, propyl paraben, butyl paraben, heptyl paraben and benzyl-paraben etc.*) are the most widely used preservatives in cosmetic, pharmaceutical, and several other industrial products including food stuffs. The term 'paraben' refers to a group of alkyl esters of para-hydroxybenzoic acid, which vary from one another at the para position of the benzene ring due to different chemical substitutions [1]. Since their initial introduction in the early 20th century, parabens have become the most regularly used preservative (not vehicle) in drugs and cosmetics around the world.

In general, parabens may be found in creams, pastes, oils, fats, glues, food, and cosmetic items [2]. Besides water, methyl and ethyl parabens stand out as widely utilized chemicals in cosmetic formulations like moisturisers, emollients, hypopigmentation agents etc. Their use is prevalent because they are cheap, colourless, odourless, and generally presumed to be nontoxic by common population. They possess stability and efficacy across a diverse pH range, coupled with a broad spectrum of antibacterial action. Additionally, their chemical stability and biodegradability further contribute to their appeal and justify their utilization [3].

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The preservative effects of parabens are caused, at least in part, by disruptions in membrane transport and mitochondrial activity in microorganisms, thereby increasing the shelf life of any substance [4]. The toxicological profile i.e. ADME and health effects of parabens are summarized in Figure 1. However, the major routes of exposure to these substances are dermal and oral, especially concerning cosmetic and food products, respectively. Parabens can reach the systemic circulation through oral ingestion or transdermal penetration, as evidenced by the measurement of systemic paraben concentrations after exposure to these chemicals [5]. On the other hand, parabens are quickly converted to p-hydroxybenzoic acid by esterases in the liver and in the skin, followed by elimination via urine [6]. The majority of parabens are excreted as glycine, sulfate, and glucuronide conjugates [7]. Carboxyl esterase enzymes present in the skin and subcutaneous fat partially metabolize topically applied parabens. These esterases hydrolyse parabens into para-hydroxybenzoic acid and respective side chains [8]. While esterases localized to keratinocytes are more active against parabens with longer chains, the carboxyl esterases found in subcutaneous fat are more active against those with shorter chains. Due to quick intestinal and hepatic metabolism, the topical use of paraben-containing components is more likely to contribute to systemic paraben levels than oral ingestion [9]. This idea is supported by the fact that the majority of human paraben exposure occurs as a result of the widespread use of personal care products.

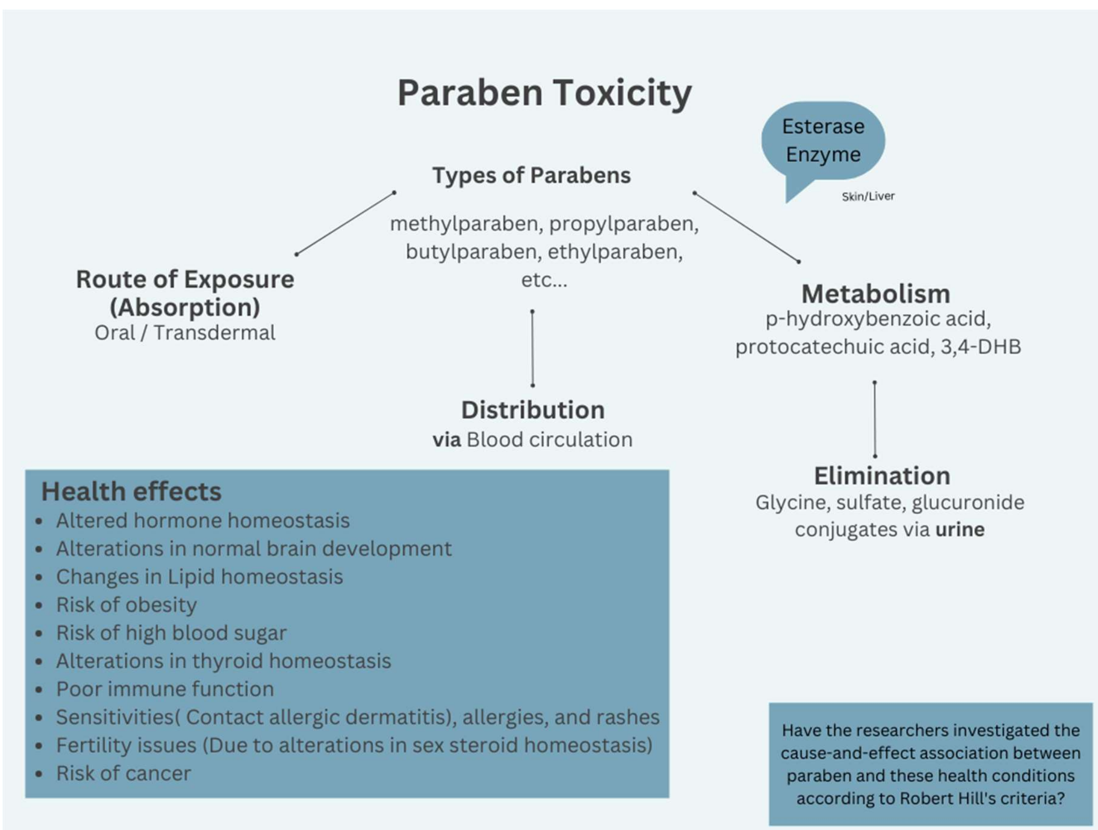

Figure 1. Absorption, Distribution, Metabolism and Elimination of Parabens & Health effects.

It was previously believed that parabens absorbed by the body were completely metabolized by esterases in the liver (and kidney in some animal species), and excreted in the urine, and did not build up within the body. However, in a study, para-hydroxybenzoic acid (PHBA), the primary metabolite of parabens, was found in all patient blood and milk samples, while individual parabens were not found in either [10].

Parabens, recognized as endocrine disruptors, have been extensively studied for their links to disruptions in estrogen hormone action [6]. In recent decades, significant research has focused on their potential estrogenic activities, leading to a concerted effort to replace them with available alternatives [11]. Due to their structural similarity to the estrogen molecule, parabens interfere with nuclear receptors for androgens, estrogens, progesterone, glucocorticoids, and other hormones, classifying them as endocrine-disrupting chemicals (EDCs). Studies on humans and rats have shown how parabens affect steroidogenesis and the activity of enzymes responsible for metabolizing endogenous hormones.

Beyond causing diseases in the reproductive and nervous systems potentially effecting normal development of a foetus, parabens also trigger skin allergies, thyroid-related issues, and malignancies by disrupting hormone function [12,14]. Extensive research in recent decades has linked parabens to disruptions in the activity of the estrogen hormone as already stated [5]. The investigation into their estrogenic properties intensified after the identification of unconjugated parabens in breast cancer cells. This sparked unwarranted concerns and speculation linking parabens with breast cancer [13].

Some studies assessed the risk of propyl- and butylparaben, revealing impacts on testosterone levels and sperm count in rats exposed to these chemicals in their diet for four and eight weeks, respectively. Propylparaben specifically led to a daily decrease in testis sperm production at dosage levels around 10, 100, and 1000 mg/kg bw/day, with the epididymal sperm count affected at 100 mg/kg bw/day [15]. Notably, commonly used parabens exhibit varying degrees of estrogenic activity in different test methods both in vitro and in vivo. Longer paraben chains and branched alkyl chains correspond to increased estrogenic activity. Additionally, PHBA demonstrates estrogenic action in both in vivo and in vitro tests. A uterotrophic experiment in mice investigated sensitivity to butylparaben exposure, considering reported in vivo estrogenic effects and known strain variations in susceptibility to endocrine disruption [16]. Some research reported the ability of propylparaben and butylparaben to cause DNA damage detectable in comet assays and induction of chromosome aberrations together with sister chromatid exchange [5].

Several studies reveal parabens' estrogen agonist properties, androgen antagonist activity and enzyme inhibition. The estrogenic activity of parabens increases linearly from methylparaben to n-butylparaben, and they can inhibit sulfation of estrogen through the inhibition of SULTs (sulfotransferase enzymes). Maternal exposure to butylparaben during gestation and lactation has been linked to reproductive disorders in male offspring [5]. Propylparaben is associated with earlier menstruation, while methylparaben is linked to earlier breast development, pubic hair development, and menstruation in girls aged 9 to 13 [17].

Overall, the impact of parabens on the Hypothalamo-Pituitary-Gonadal-Axis, influencing secondary sexual characteristics, menstruation duration, sperm quality, and their effects on estrogen-dependent breast cancer cells, as well as Hypothalamo-Pituitary-Thyroid axis in pregnant and nursing mothers (resulting in elevated TSH, TT3 levels and higher birth weights in boys concerning), and transplacental spread etc. remains a subject of vigorous debate within the core scientific community and medical fraternities of the Western world. The need for more in-vivo data and well-planned studies had been stressed by researchers and medical doctors time and again [18]. By the same token, there has been enough discussion on the local effects of parabens being used in dermatological and ocular drug preparations. The health issues concerned range from irritation, dermatitis (allergic/contact), a risk factor for depigmentation disorders and skin cancers (basal cell carcinoma and melanomas) [19]. Interestingly, several dermatological associations have advocated the need for research on systemic effects rather than local effects, as parabens rarely cause acute and local effects, and most of the purported effects are chronic and long-term [20-22]. For the sake of clarity, the cutaneous manifestations of toxicity include inflammation, corrosion, contact dermatitis, ageing etc. to name of few.

Similarly, there have been occasional discussions both in favour of and against exploring economically viable and pro-health alternatives to parabens. Simultaneously, there is a cautious approach towards abandoning parabens, given their established relative safety, as toxicology data for newer preservatives is yet to be ascertained. Additionally, the consideration of using paraben free products with a shorter shelf life that are more human and ecologically friendly has been contemplated; especially during pregnancy and lactation owing the fact that research demonstrated effects of paraben on maternal and child thyroid health. The persistence of parabens in the environment has also been a topic of discussion, including considerations on how to remediate their impact [21,22,23].

Conflicting evidence persists in the literature regarding the impact/effect of parabens on thyroid hormones, with uncertainties surrounding whether they lead to an increase or decrease in hormone levels. Most studies have shown elevated TSH levels in children and decreased T3 and T4 levels in adults. The data on pregnant women is sometimes conflicting at different periods of gestation. For example, some studies indicate raised TSH during early pregnancy and decreased TSH between 16-20 weeks, while a few studies showed increased T3 levels, a majority showed decreased T3 and T4 levels. It is acknowledged, however, that parabens influence thyroid homeostasis. Similarly, their effects, such as pro-estrogenic, anti-androgenic, adipogenic, and carcinogenic impacts in humans, necessitate methodological validation or refutation on a global scale through multilateral cooperation [22].

Although some systematic reviews have been conducted in this area of research, the reliability of results out of these reviews is compromised due to the majority of them lacking specificity for humans. The overall quantity and quality of published literature studying the association between parabens and human health (leaving aside in vitro, in vivo, in silico papers) is insufficient for establishing a higher level of evidence using systematic reviews or meta-analysis. The limited number of clinical studies, mostly comprising birth cohort studies or investigations on adolescents, expectant and lactating women, focuses on the mere presence of parabens and their metabolites in body fluids and the observed alterations in endocrinological markers, such as hormones and hormone precursors and often times the studies include a cocktail of potential endocrine disruptors.

Some of these studies lack methodological rigor, as they often fail to properly account for very essential 'host' and 'environmental' factors. Moreover, the concept of 'endocrine disruption' may seem just fancy in the realm of 'evidence-based medicine' when a clinical sign/symptom/disease is not evident in the study population. A causal association or potential link goes beyond the mere presence of a substance and changes in hormone levels. Paraben toxicology in medicine requires more emphasis on clinical endpoints rather than solely relying on laboratory values.

The considerable variability in hormone assessment results, at times conflicting, is influenced by factors like the method used, calibration, timing of sample collection, individual health conditions, and various other uncontrolled variables. Unfortunately, many studies have not adequately addressed these factors, compromising their reliability for making assessments or establishing links to specific diseases.

In India, the use of parabens in drugs and cosmetics is governed by BIS Standard IS 4707 (Part 2): 2017, along with relevant provisions of the Indian Pharmacopeia. Meanwhile, the Food Safety Standards Authority of India (FSSAI) regulates the use of parabens as a food additive in the country. Stricter regulations on parabens are observed in the European Union (for example in the EU: The maximum total concentration allowed in such consumer products is 8 g of parabens per kg of cosmetic product, with no single paraben having a higher concentration than 4 g/kg. for longer paraben molecules; the maximum concentration of 1.9g/kg)[24], Canada and the USA. These countries have established comprehensive frameworks overseen by regulatory bodies such as the European Commission, the U.S. Food and Drug Administration (FDA), and Health Canada, ensuring adherence to specified limits and safety standards for the use of parabens in drugs, cosmetics, and food products.

Concerns in Indian Context:

1. Limited research has been conducted on the impact of preservatives, such as parabens, in personal care products on the Indian population, as evident in the scarce literature [25]. It is imperative to initiate well-structured studies in our country to comprehensively understand the effects of these preservatives.
2. A comprehensive investigation into chronic paraben toxicity necessitates interdisciplinary collaboration, involving endocrinology, dermatology, paediatrics, and obstetrics departments. Establishing baseline levels of parabens and their metabolites within the Indian population and environment is crucial for informed toxicological assessments.
3. Delving into toxicogenomic considerations pertaining to both dermal and systemic metabolism of parabens specific to the Indian population is vital for unravelling potential genetic susceptibilities.
4. Exploring the potential influence of skin and gut microbiomes on paraben toxicology in the Indian population is paramount for a

holistic understanding of the molecular mechanistic toxicology of parabens.

5. Current regulations lack consideration for cumulative exposure in defining permissible limits for substances. Investigating and rectifying this oversight is essential for a more comprehensive approach to risk management.
6. A multi-centric research initiative at Indian medical colleges is essential to decipher the role of confounding variables influencing associations between parabens and various health conditions.
7. The Department of Health Research, Government of India should consider adopting a comprehensive approach, aligning with Hill's criteria of causation for investigating the association between paraben and putative health conditions. Both clinical and epidemiological datasets are imperative to unravel the intricacies of this subject matter.
8. The professional associations of the specialities of paediatrics, endocrinology, obstetrics, and dermatology should collaborate to establish a working group. This group can issue a position paper, consolidating scientific knowledge on the toxicity of parabens and frame proper research questions and methods to work out them scientifically.
9. In light of the burgeoning industry of paraben-free products in India, research endeavours are warranted to inform public choices and address broader public health concerns.
10. Inclusion of parabens and their toxicology in the medical curriculum is essential for enhancing the knowledge base of healthcare professionals and researchers in our country.

In conclusion, it is a categorical imperative for our scientific community to actively engage in the ongoing global discourse surrounding paraben toxicity. The existing body of clinical research appears inconclusive and appears to lack the prescribed scientific rigor. We believe that the Indian scientific community, with the collaboration and support of healthcare professionals, is well-positioned to address the unresolved questions pertaining to paraben toxicity. This is not merely an academic debate but holds significant implications for public health, particularly given the substantial population in our context that utilizes cosmetic products, drugs containing parabens as preservatives, and certain foods preserved with parabens. It is high time to prioritize and launch comprehensive research initiatives to guarantee the safety of our citizens, with a particular focus on high-risk groups such as pregnant women and children.

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Conflict of Interest

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