ORIGINAL RESEARCH ARTICLE

Could the high incidence of breast cancers in Nigerian women be related to 1,4-Dioxane in skin lightening products?

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Abstract
Two monstrous female health-related issues are currently engaging the attention of the global community. These are the chemical skin-lightening issue and the rising female breast cancer issue. Nigeria has the highest prevalence of chemical skin lightening practice with 77.3% of traders in Lagos using such products and one of the highest incidences of breast cancer globally of 50.5 per 100,000 women. 1,4-Dioxane, a possible contaminant in toiletries and cosmetics, is an IARC group 2B carcinogen and a potential breast carcinogen. It is generated when ethylene oxide -a known breast carcinogen is added to other chemicals during manufacturing. The skin lightening procedure is most conducive for optimal per-cutaneous absorption and inhalation of Dioxane. The research question entertained was if there is a link in the increasing prevalence of skin lightening practice and the rising breast cancer burden in Nigeria. One hundred skin lightening products procured from across Lagos, Nigeria had their listed contents scrutinized and entered onto a spreadsheet, then they were analyzed for Dioxane using Scalia’s Solid Phase Extraction gas chromatography procedure. Water (Aqua) 66%, Glycerin 60% and Tocopherol or Vitamin E 41% were found to be the most listed ingredients on the package labels, with Vitamin C 28%, Kojic acid 26%, Citric acid 22% and Carrot oil seen in 20% of products. All the analyzed samples were negative for Dioxane. The study brought to the fore the need to explore other potential breast carcinogens in skin lightening cosmetics and environmental chemicals.

Keywords: Breast cancer; 1,4-Dioxane; skin lightening; carcinogen

Introduction
Nigeria has about the world’s highest percentage of women engaged in skin lightening. According to the World Health Organization, 77% of women sampled in an urban market in Nigeria use skin lightening products.1 Globocan’s 2018 cancer statistics show increasing incidence rates in Nigeria with 50.5 per 100,000 woman in 2012 and a projected estimated 84.2 per 100,000 women by the year 2030.2,3 Breast cancer incidence rates are highest among Non-Hispanic White women, with non-Hispanic Black women (of which category Nigerian women fall) having the next highest incidence. Despite having a lower incidence rate compared to non-Hispanic White women, non-Hispanic Black women have a lower cancer survival rate due to a combination of factors such as aggressive tumor
biology, younger patients, late stage of diagnosis, lack of access to treatment, to name a few.\textsuperscript{3,4} Though Nigeria is second only to Mauritius with regards breast cancer incidence in Africa (50.5 per 100,000 and 64.2 per 100,000 woman per year respectively), her age-standardized mortality ratio was highest in Africa (25.9 per 100,000, compared to 18.8 per 100,000 for Mauritius).\textsuperscript{2,3} It is instructive to note that Africa and indeed Nigeria suffers from data unavailability with few cancer or other disease registries, thus the alarming figures above may be an underestimation. There is need to urgently identify the prevalent risk factors, biological and environmental which may be associated with the rising incidence of breast cancer in Nigerian women.

1,4-Dioxane is classified as a group 2B carcinogen and a potential breast carcinogen\textsuperscript{5} according to the International Agency for Research on Cancer (IARC). 1,4-Dioxane or 1,4-diethyleneoxide, is simply called Dioxane, because the 1,2- and 1,3- isomers of dioxane are rare.\textsuperscript{6} The Environmental Protection Agency considers 1,4-dioxane a probable human carcinogen, based on the “induction of nasal cavity and liver carcinomas in multiple strains of rats, liver carcinomas in mice, and gall bladder carcinomas in guinea pigs.”\textsuperscript{7} Dioxane is not a skin bleaching ingredient, but may be found in as many as 22 percent of the more than 25,000 cosmetics products in the Skin Deep database but usually not indicated on ingredient labels because it is a contaminant created when common ingredients are mixed together.\textsuperscript{8} Dioxane is generated through a process called ethoxylation, in which ethylene oxide, a known breast carcinogen, is added to other chemicals to make them less harsh.\textsuperscript{8} Dioxane differs from dioxin (or dioxins), which are persistent organic pollutants in the environment produced as byproducts of burning or industrial processes.\textsuperscript{9} Dioxane is used as a solvent in a wide range of organic products: lacquers, paints, varnishes, paint and varnish removers, wetting and dispersing agent in textile products, dye baths, stain and printing compositions, cleaning and detergent preparations, cements, cosmetics, deodorants, fumigants, emulsions, and polishing compositions.\textsuperscript{5}

During showering, bathing, or laundering, dioxane in tap water may volatilize and expose one to dioxane vapors.\textsuperscript{10} Adverse effects of dioxane are not only relevant to the users of the cosmetic products but may affect others via inhalation. This is akin to passive smoking by those who do not smoke but inhale tobacco smoke with all the inherent dangers such as production of the biomarker cotinine, which is formed after nicotine enters the body.\textsuperscript{11} Dioxane was found unsafe for use and banned in cosmetics in Europe\textsuperscript{12} and Canada.\textsuperscript{13} In 2008, tests sponsored by the US Organic Consumers Association found dioxane in about half of tested organic personal-care products.\textsuperscript{8,10} Since 1979, the FDA conducted tests on cosmetic raw materials and finished products for the levels of dioxane. Dioxane was present in ethoxylated raw ingredients at levels up to 1410 ppm, and at levels up to 279 ppm in off the shelf cosmetic products.\textsuperscript{10} The researchers concluded that levels of 1,4-dioxane in excess of 85 ppm in children’s shampoos indicate that continued monitoring of raw materials and finished products is warranted.

**Statement of the problem**

A high proportion of the skin-lightening products in Nigeria are customized products mixed for individuals and beauty Spas. There are online schools where the art of “mixing ingredients” are taught. The skin lightening procedure is most conducive for optimal per-cutaneous absorption and inhalation of 1,4-Dioxane. It is critical to note that exposure to toxic chemicals which may be found in cosmetics or in the environment is not only through skin contact. Some of these chemicals are transmissible trans-placentally to the unborn child, through breast milk to a baby, through inhalation, injection, ingestion in drinking water and or food chain. Several other factors are relevant to effect toxicity—dose, route of exposure, timing and frequency of exposure, habits, presence of other chemicals and genetic factors contribute to the overall susceptibility to breast cancer development.\textsuperscript{8,10}
The bleaching process is subsequently maintained through daily application of bleaching creams and periodic (3-6 monthly) “Body Works” for decades. The environmental tropical hot and humid climate further enhances percutaneous absorption. Vulnerable populations are pregnant women, infants and adolescents. The IARC uses the term “agent” when classifying carcinogens and it encompasses both substances and exposure circumstances that pose a risk. Therefore, for skin-lightening practices, both the chemicals and all the exposure circumstances discussed are regarded as “agent”.

The research question we sought to answer was – Is there a possible link between the skin lightening practice and the raging breast cancer burden in Nigeria? This led to the analysis of a broad spectrum of skin lightening products for the presence of 1,4-Dioxane

Aim
The aim of the study was to assay for the presence of 1,4-Dioxane in a spectrum of skin-lightening products used by women in Nigeria.

Objectives
1. To identify the ingredients listed in common skin lightening cosmetics sold across the Lagos Metropolis
2. To determine the frequency of known skin lightening ingredients in the cosmetics sold across the Lagos Metropolis
3. To determine the presence of 1,4-Dioxane in skin lightening cosmetics sold in Lagos

Materials and Methods
This was a cross-sectional analytic study of skin cosmetics liberally sold in open markets, supermarkets and upscale spas in selected communities in the Lagos Metropolis. The study was in two parts: the procurement of the cosmetics with identification of the listed ingredients on the package and analysis for 1,4-Dioxane in the cosmetics using Gas chromatography coupled with a Flame Ionization Detector (GC-FID).

The Lagos metropolis is geographically divided into the Mainland and the Island by the lagoon. An open market, a busy super (hyper) market and a spa on both the mainland and Island were selected randomly from a generated list of all available markets and stores in the local community.

One hundred (100) cosmetics in lotions (38), creams (26), soaps (23), serums (11), body milk (10) and gels (6) marketed as skin lightening, brightening, whitening, clarifying and toning were purchased from open markets where the low socio-economic classed indigenes shop, a few upscale supermarkets and beauty spas across Lagos metropolis as well as through the internet. Fourteen soap and lotion preparations of the same products were sampled to ascertain consistency of active ingredients across different vehicles. The samples included a broad spectrum of both high-end and bootleg versions purchased from assorted sale outlets in Lagos, Nigeria. The contents as listed on the package labels were entered onto a spreadsheet before handing over all cosmetics as procured to the scientists at the Nigerian Institute for Oceanography and Marine Research (NIOMR)- our collaborators in this research where further analysis of 1,4-Dioxane in the cosmetics was done using Scalia’s Solid Phase Extraction procedure. The procedure used matrix-specific extraction, analyte-specific clean-up and a Gas Chromatograph coupled with a Flame Ionization Detector (GC-FID). After solid-phase extraction using Bond Elut silica, Bond Elut C18 disposable cartridges and an internal standard mix of 2-Chloroacetonitrile, Hexafluoro-2-methyl-2-propanol and Hexafluoro-2-
propanol, samples were injected directly into Agilent 7820A GC-FID that had been Calibrated with 1,4-dioxane Standard. The flow chart of the extraction process is shown in Figure 1 below.

The recovery of the method was determined by analyzing a sample each from the three matrices spiked with 100,150 and 200mg/kg of 1, 4-dioxane respectively. Repeatability was estimated by running one out of every 10 samples from the total number of samples (n100) as a duplicate; making at least 10 duplicate analyses.

![Flow chart of the extraction procedure](image)

**Figure 1: Flow chart of the extraction procedure**

**Result of study**

In 100 cosmetics reviewed, Water (aqua) and Glycerin were the two most listed ingredients on the package labels at 66% and 60% respectively. Hydroquinone was listed in 14% of the products with a stated concentration of less than or 2% in 10 of the products. Mid to high potent corticosteroids - Betametasone dipropionate and Clobetasole propionate were listed in 4% of products. Other ingredients are as shown in Figure 2. Fifteen percent of the sampled products were made in Nigeria while the remaining 85% of the products were imported from outside Nigeria. Figures 3 & 4.

Three different products had Clobetasol propionate as the major ingredient with other excipients and 1 gel had Betamethasone dipropionate as its only ingredient without any excipients. One product which was listed to be a cream, serum and body milk had more than 10 active ingredients as well as Sodium lauryl sulphate and the antifungal-Ketoconazole cream in the mix.
Figure 2: Frequency of ingredients listed on skin lightening cosmetics

Figure 3: Pie chart showing the proportion of continents where skin lightening cosmetics were manufactured.
Subjecting the products to gas chromatography, 1, 4-dioxane was not detected in all the commercial cosmetic products investigated. Recovery of 1, 4-dioxane from different cosmetic matrices was between 61.30% and 100.30%. (Figure 5) The minimum quantifiable amount was 29.7mg/kg, while the limit of detection was 8.9mg/kg. 1, 4-dioxane has been found as an impurity in cosmetics, household and industrial detergents, and pharmaceuticals due to its occurrence as a by-product in ethoxylated emulsifiers.

**Discussion**

The practice of skin lightening is rampant in Africa, and Nigeria especially. The products and processes used to lighten the skin have become more minimally invasive through BodyWorks with possible biological and environmental changes which may only be seen after many years. The rising incidence of breast cancer in Nigeria with increasing mortality may be associated with Dioxane - a potential breast carcinogen released into the environment when cosmetics are mixed in the skin lightening procedure considering similar demographics and the trend in mortality. Though
Dioxane was not seen in any of the 100 skin lightening products analysed, many of the cosmetics had alpha hydroxy acids which can be potentially toxic especially with increased percutaneous absorption.\textsuperscript{17}

This study found that water was the most listed ingredient in 66\% across all vehicles-whether lotions, creams, gels, or soaps; with glycerin coming a close second at 60\%. Considering that water is a major excipient in almost all cosmetics and personal care products,\textsuperscript{18} it is presumable that some manufacturers decide not to list it on their ingredients. This is however not the correct practice because everything used should ideally be listed. The other glaring thought will be that if the manufactures fail to list water (aqua), what else are they not declaring? Glycerin is another common ingredient in cosmetics because it is hygroscopic and acts as a humectant, drawing water from the air and deeper skin layers to the top of the skin. It is a vehicle which potentiates absorption of other active ingredients in the cosmetic. It is generally considered safe at approved concentrations.\textsuperscript{19(36)}

The listed ingredients however do not often give the concentrations used in the package list thus one cannot objectively infer the safety of the products. Vitamin E was declared in 41\% of the products in this study. This fat-soluble vitamin is an excellent antioxidant which must be obtained from a diet rich in nuts, spinach, whole grains, olive oil to mention a few. It oxidizes slowly when exposed to air thus topically applied Vitamin E is most unstable in air and light and not very effective. With these skin lightening products sold in open markets, exposed to the elements in this tropical Nigerian climate, the chances of buying and applying inert or rancid products is high.\textsuperscript{20}

About a quarter of the products (20-26\%) declared various alpha hydroxy acids (AHAs) such as Kojic acid, Ascorbic acid, Citric acid and carrot oils in their list. These are mostly weak acids which serve to increase shedding of surface skin or exfoliation. The degree of shed is dependent on the concentration of the acid and the resultant increase penetrance of other substances.\textsuperscript{21} The United States Food and Drug Agency (FDA) has set a limit in the concentration of what can be placed in a non-prescription cosmetic, with any increased concentration taken as a drug.\textsuperscript{22} It behooves on the manufacturers to declare the concentration, so consumers are guided. Hydroquinone was declared in 14\% of the cosmetics reviewed. This is a relatively low figure when compared with the frequency of AHAs found. Hydroquinone has been adversely touted alongside mercurial with respect to dangers of skin lightening for many years. It is possible that manufacturers no longer declare it on their product list. However, a recent study by Egbi and Kasia in an undergraduate university in Bayelsa State, Nigeria reported 42.7\% of the skin lightening agents employed was Hydroquinone - with undeclared concentration.\textsuperscript{23(38)}

About half of the cosmetics were manufactured in Europe and imported into Nigeria, with 15\% of the products being manufactured in Nigeria. This is an interesting finding considering the laws or rules regarding these cosmetics in the European Union (EU) /EEC countries.\textsuperscript{12} Products made in Nigeria are ideally subjected to the protocols of the Nigerian Agency for Food and Drug Administration and Control (NAFDAC) for verification, but there are many products being compounded by charlatans and unlicensed personnel which are sold freely on the internet and even in the open market. Periodically, the officials of NAFDAC clear them off the shelves, but they tend to find their way back because of weak legislations and lack of enforcement.

Dioxane was not found in the analysis of any of the products. This may be explained by the fact that it is not a constituent of skin lightening or bleaching cosmetics, but often detected when cosmetics are mixed.\textsuperscript{6,8} The gas chromatography employed was done on the actual products,\textsuperscript{16} but it is known that most people who bleach their skin use multiple products. Perhaps if the analysis was done on a mixture of two or more of the cosmetics, there may have been a higher level of detection. Also, most manufacturers currently utilize vacuum stripping to remove 1,4-dioxane before formulation of ethoxylated surfactants in consumer cosmetics and household products.\textsuperscript{24} Theoretically, Dioxane
is produced as a byproduct in ethoxylation reactions and detected as a contaminant. Levels of contamination may also be very low as to escape detection and it is the gradual accumulation of these contaminants in the environment which is implicated in the carcinogenic process. Over the years, there has been a decline in the detection of 1,4-dioxane in cosmetic products. The International Cooperation on Cosmetics Regulation (ICCR), the Campaign for Safe Cosmetics and the Organic Consumers Association reported non-detection of 1,4-dioxane in a larger percentage of samples investigated. This compares with the outcome of this present investigation where 1,4-dioxane was not detected in any of the samples investigated.

There are other sources of exposure to 1,4-dioxane outside the skin lightening products which we analyzed in this study. There may be need for further research in the presence of dioxane in household cleaning products, other cosmetics, fragrances and the likes already listed above. Continued periodic monitoring of ethoxylated cosmetic raw materials and cosmetic finished products for the presence of 1,4-dioxane is necessary.

Besides Dioxane, the other known potential breast carcinogens, in skin lightening products are Methylmercury, Hydroquinone, Trimethylamine (TMA), N-Nitrosodimethylamine (NDMA), Oxybenzone and heavy metal contaminants. Akortha et al performed mutagenic and genotoxic screening of eight commonly used skin whitening creams in Nigeria. The results of the study revealed that all eight skin whitening creams were mutagenic in bacteria and could be said to possess carcinogenic potentials.

The current rage in skin bleaching in Nigeria started in the 1960s and the chemicals that were used at that time were mercury derivatives and hydroquinone in high doses. There is another group of “unclassifiable” people who use the home-made concoctions literally made from raw versions of known carcinogens already listed above. These concoctions are used even on babies, children and adolescents. It has been reported that women intensify the application of the skin lightening products during pregnancy to reduce the physiological hormone-induced generalized hyper-melanosis associated with pregnancy. This intensified use of the products during pregnancy obviously translates to enhanced fetal dose of chemical carcinogens which are transmissible trans-placentally. Studies also found that young girls in Nigeria and some other African countries start the use of the skin lightening products in adolescence to enhance their marriage prospects, and some mothers encourage them to bleach their skin by funding the purchase of the products, increasing exposure to chemicals at puberty. The possible relationship between breast cancer and skin bleaching products is evidently complex and would require a prospective longitudinal study.

**Conclusion**

This study did not find 1,4-Dioxane in any of the skin lightening cosmetics analysed. Vitamin E (tocopheryl acetate) and the alpha hydroxy acids were listed in several of the cosmetics. It is instructive to note the other sources of exposure to 1,4-dioxane outside the skin lightening products which were analyzed in this study. There is need to explore other potential breast carcinogens in skin lightening products and some other environmental chemicals already identified though animal and epidemiological studies as mammary gland toxicants. Continued periodic monitoring of ethoxylated cosmetic raw materials and cosmetic finished products for the presence of 1,4-dioxane is necessary.

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**Acknowledgments**

We are grateful to FAMFA Oil Nigeria Ltd for graciously funding the work.

We thank Mr Gabriel Ogor, who typed the manuscript.