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Strengthening the Surveillance of 1,4-Dioxane Contaminants in Cosmetics through Harmonization of Analysis Methods and Networking of Cosmetics Laboratories in Indonesia

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ABSTRACT / ABSTRAK

Laboratories play a strategic role in protecting public health by ensuring the quality and safety of drugs, food, and cosmetics. The Centre of National Quality Laboratory of Drugs and Food (CNQLDF), as the central laboratory of the Indonesian Food and Drug Authority (Indonesian FDA), continuously develops reliable, selective, sensitive, and accurate analytical methods (AM) for cosmetic testing in line with advancements in cosmetic formulation technology. However, both the Indonesian FDA and external cosmetic laboratories need more human resources and infrastructure, hindering the development of analytical method and the testing of cosmetic products. Strengthening these laboratories through stakeholder networks is essential. Indonesia actively participates in the ASEAN Cosmetic Testing Laboratories Committee (ACTLC) and the Indonesian Cosmetic Laboratory Network (ICLN). One of the main tasks of CNQLDF is to develop a new ASEAN Cosmetic Method (ACM) for 1,4-Dioxane contaminants in cosmetics. Currently, CNQLDF, along with the Indonesia National Standard Body (INSB), Ministries and External Laboratories, in which together became members of ICLN, harmonized the analytical method of 1,4-Dioxane at the national level, leading to the issuance of the Indonesian National Standard (INS). Both the INS and ACM have main purpose to standardize analytical methods across laboratories, ensure the safety and quality of cosmetic products and enhance national product competitiveness. This study examines method to strengthen pre-market cosmetic surveillance through harmonizing the analytical method of 1,4-Dioxane at the national and ASEAN regional levels, using a qualitative approach based on the Indonesian FDA's internal data and stakeholder information on 1,4-Dioxane testing capabilities.

Laboratorium mempunyai peranan yang sangat strategis dalam melindungi kesehatan masyarakat dengan menjamin mutu dan keamanan obat dan makanan, termasuk kosmetikyang beredar di masyarakat. Pusat Pengembangan Pengujian Obat dan Makanan Nasional (PPPOMN) sebagai laboratorium pusat Badan Pengawas Obat dan Makanan (BPOM) terus mengembangkan metode analisis (MA) pengujian kosmetika yang handal, selektif, sensitif dan akurat seiring dengan perkembangan teknologi formulasi kosmetik. Namun, hingga saat ini laboratorium kosmetik, baik di Badan POM maupun laboratorium eksternal masih dihadapkan pada keterbatasan sumber daya manusia maupun sarana dan prasarana dalam melakukan pengembangan MA dan pengujian sampel produk kosmetik yang beredar. Untuk itu diperlukan perkuatan laboratorium pengujian kosmetikantara lain melalui jejaring dengan melibatkan stakeholder terkait. Saat ini jejaring laboratorium pengujian kosmetik yang sudah diikuti oleh Indonesia secara aktif adalah ASEAN Cosmetic Testing Laboratories Committee (ACTLC) dan Jejaring Laboratorium Kosmetik Indonesia (JLKI). Salah satu peran

Indonesia di ACTLC dalam hal ini didelegasikan kepada PPPOMN adalah menjadi negara yang bertanggung jawab dalam pengembangan MA cemaran 1,4-Dioksan dalam kosmetik menjadi ASEAN Cosmetic Method (ACM) yang baru. Saat ini PPPOMN dan BSN serta Kementerian dan Laboratorium Eksternal yang tergabung dalam JLKI sedang berproses melakukan harmonisasi MA 1,4-Dioksan pada tingkat nasional berupa penerbitan Standar Nasional Indonesia (SNI). Dengan adanya SNI dan ACM ini seluruh laboratorium memiliki metode analisis standar untuk menjamin keamanan dan mutu produk kosmetik yang beredar serta meningkatkan daya saing produk bangsa. Penelitian ini dilakukan untuk mempelajari metode penguatan pengawasan pre market kosmetik oleh industri dan laboratorium eksternal melalui harmonisasi MA 1,4 Dioksan di tingkat nasional maupun regional ASEAN.. Penelitian ini disusun dengan menggunakan pendekatan metode kualitatif berdasarkan data internal BPOM maupun data stakeholder yang terkait regulasi dan kemampuan pengujian 1,4-Dioksan tingkat nasional maupun regional.

Keywords: 1,4-Dioxane, Cosmetic, Pre-market Surveillance, Laboratory Network, Indonesian FDA
Kata Kunci: *1,4-Dioksan, Kosmetik, Pengawasan Pre-market, Jejaring Laboratorium, BPOM*

1. Introduction

As the backbone of drug and food control, laboratories have a strategic role in ensuring the quality and safety of drug and food products circulating in the community, including cosmetic products. Cosmetics are one of the commodities inherent in our daily lives, from the moment we wake up until we go back to sleep. This suggests that cosmetics have become a fundamental necessity for individuals of all ages, encompassing both women and men. With the advancement of cosmetics industry technology, ease of transportation, and access to information today, more diverse types of cosmetics are circulating in the community, with innovations in various formulations. To protect the public from cosmetics with health risks, the Indonesian FDA conducts comprehensive supervision starting from pre-market evaluation in the form of product notification before marketed in the national market to post-market control or when the product is circulated in the community. The extensive process of cosmetic product supervision generally starts with preparing standards, registration or notification, inspection or examination of facilities and products, laboratory testing, and law enforcement (Indonesian FDA Regulation No. 21/2020).

The Indonesian FDA Regulation No. 21/2022 on the Procedure for Submitting Cosmetics Notification states that every cosmetic product distributed in the territory of Indonesia must have a distribution permit in the form of a notification from the Head of the Indonesian FDA. Until October 2023, around 471,121 cosmetic products were notified at the Indonesian FDA, positioning it at the first rank in Indonesia's registered food and drug products. This is a challenge for cosmetics testing laboratories to build capacity and test capabilities to ensure the quality and safety of cosmetic products in circulation BPOM, 2022).

One of the efforts to answer these challenges, the Centre of National Quality Laboratory of Drugs and Food (CNQLDF) continues to develop analytical methods for cosmetics testing, both simple and sophisticated techniques, resulting in the test being carried out quickly, accurately, effectively and efficiently. However, to date, cosmetic laboratories, both at the Indonesian FDA and external laboratories, have the same obstacles

regarding limited resources in developing analytical methods and testing cosmetic product samples, as well as both human resources and testing infrastructure. Therefore, it is necessary to strengthen the cosmetic testing laboratory, among others, through networking by involving relevant stakeholders to synergize in improving public health protection from health-threatening cosmetic products. This aligns with the penta helix model of drug and food supervision as the key to the more effective drug and food supervision by involving five elements including business actors, the community like non-governmental organizations, government, academics, and the media (BPOM Regulation No. 9 of 2020).

Indonesia has actively participated in the regional cosmetics testing laboratory network, the ASEAN Cosmetic Testing Laboratories Committee (ACTLC). ACTLC is one of the committees of the ASEAN Cosmetic Committee (ACC) working group. ACTLC's main task including to conduct studies or develop analytical method related to ingredients that are or will be created for use and prohibited ingredients in cosmetics by the ASEAN Cosmetic Directives (ACD).

In the ACTLC network, Indonesia represented by CNQLDF, was responsible for developing the analytical method of Determination of 1,4-Dioxane in cosmetics, which is currently already published as a new ASEAN Cosmetic Method (ACM). The 2019 Indonesian FDA regulation on contaminants in cosmetics categorizes 1,4-Dioxane as a chemical contaminant, a hazardous substance from chemical elements or compounds that can harm and endanger human health. 1,4-Dioxane is a contaminant produced as a by-product in manufacturing certain cosmetic ingredients. It is produced when ethoxylated chemicals are used in cosmetic products. During the ethoxylation or alkoxylation process, unwanted side reactions may accidentally produce 1,4-Dioxane. 1,4-Dioxane is commonly found in products with PEG, polyethylene, polyethylene glycol, polyoxyethylene, -ethylene (e.g., laureth sulfate), -et- or -oxynol- listed on the product label ((Zhou, 2019 and U.S. Food and Drug Administration, 2022). These contaminants may be present in cosmetic products such as shampoo, body wash, baby lotion, hair lotion, and bubble baths. Furthermore, in a survey conducted by the U.S. FDA in 2018, 2 out of 82 commercial products had 1,4-dioxane concentrations above ten ppm. While in a study conducted by Castor et al. (2021) stated that 53% of detergents, 59% of shampoos, 62% of body cleaners, and 69% of dish soaps contained 1,4-Dioxane above one ppm.

The risks to health from 1,4-Dioxane contamination include irritation of the eyes, nose, and throat, and can trigger kidney and liver damages (SCCS, 2015). The International Agency for Research on Cancer (IARC) and the Environmental Protection Agency (EPA) designated 1,4-Dioxane as a compound that may cause carcinogens in humans (Group 2B) in 1999 based on the results of animal carcinogenicity tests conducted through oral administration to rats, mice, and guinea pigs. According to the Scientific Committee on Consumer Safety (SCCS) in 2015, cosmetics with 1,4-Dioxane contaminant levels less than 10 ppm (g/g) are considered safe.

This study was conducted to strengthen pre-market surveillance through a network of cosmetics laboratories, mainly industrial laboratories and external laboratories, through harmonization of AM 1,4-Dioxane used for cosmetic testing. Through this laboratory network, all cosmetic laboratories are expected to have the same analysis standard, thus it prevent disputes regarding test results. The more AMs being harmonized, the more it will help stakeholders and the public ensure the safety and quality of cosmetic products in circulation. This harmonization includes the stage of method transfer to all cosmetic testing

network laboratory members, one of which is by increasing the competence of external laboratory testing staff related to the method. The strengthening of external laboratories and industry can encourage the industry to be fully responsible for ensuring its products' safety, quality, and efficacy. Thus, post-market surveillance carried out by Indonesian FDA can focus more on prohibited and restricted ingredients critical to endangering public health.

2. Methodology

This research was prepared using a qualitative method approach. The data used in this study are internal data of the Indonesian FDA and related stakeholders data in the form of primary data and secondary data, including the following data:

a. Comparison of international regulations on dioxane control from ASEAN, European Union, and America
b. The capability of laboratories in Indonesia and ASEAN to conduct 1,4-Dioxane testing
c. Development of regulations in Indonesia regarding 1,4-Dioxane from year to year
d. CNQLDF cosmetic laboratory collaboration test result data conducted in 2022

3. Result and Discussion

3.1 Description and Safety Evaluation of 1,4-Dioxane

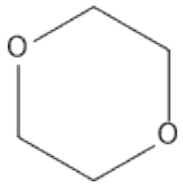

Figure 1. Structure of 1,4-Dioxane

1,4-Dioxane ($C_4H_8O_2$) is a clear liquid that dissolves easily in water. 1,4-Dioxane is commonly used as a solvent in some manufacturing processes and as a laboratory reagent. 1,4-Dioxane is a potential contaminant in some dietary supplements, water supplies contaminated with 1,4-Dioxane, cosmetics, detergents, and shampoos (Wilbur et al., 2012).

Regarding the toxicity of 1,4-Dioxane, it is classified in the European Union as a category two carcinogen (suspected of causing cancer) by IARC as a group 2B carcinogen (this agent is probably carcinogenic in humans) based on sufficient evidence of carcinogenicity in animals and insufficient evidence of carcinogenicity in humans and by the U.S. EPA in group B2 (Probable human carcinogen). Meanwhile, the U.S. NIOSH considers 1,4-Dioxane a potential carcinogen in the workplace. Based on the results of the toxicity evaluation of ingredients, (the Scientific Committee on Consumer Safety (SCCS) thinks that the level of 1,4-dioxane in cosmetic products representing LCR not more than 10^{-5} is considered safe for consumers. Thus, 1,4-Dioxane levels in cosmetic products of not more than 10 ppm are considered secure (SCCS, 2015).

Table 1. Toxicological Evaluation of 1,4-Dioxane Exposure

No	Type of Exposure	Toxicology Evaluation
1	Short-term exposure	Exposure to low levels and short periods of 1,4- dioxane may cause eye and nc irritation. Exposure to massive doses can cause kidney and liver damage and ev death.
2	Long-term exposure	Rodents: inhalation of vapors, ingestion of contaminated water, or skin contact w 1,4-dioxane, which mainly affects the nasal cavity, liver, and kidneys.
3	Possibility of Cancer	Long-term 1,4-Dioxane carcinogenicity studies in rats orally and by inhalati showed a positive correlation in the form of liver and kidney tumors or cancers. Liver tumors are believed to be related to cytotoxicity, which can be explained reactive metabolites such as HEAA and its related metabolite, hydroxyethoxyacetaldehyde.
4	Reproductive health/ baby	Miscarriages and stillbirths: There is a trend towards increased rates of spontanec abortion and stillbirth associated with occupational exposure to the combination 1,4-Dioxane with other substances. Breast milk transfer: A nursing mother exposed to high amounts of 1,4-Dioxane m pass it on to the infant through breast milk.

According to SCCS (2015), daily exposure values considered safe are presented in Table 2.

Table 2. Summary of Safety Assessment for 1,4-Dioxane

No.	Summary of Safety Assessment for 1,4-Dioxane	Daily Exposure Level Considered Safe	Type of Exposure
1	Canada – CMP assessment	85 µg/day	Aggregate exposure, 100% inhalation, 3.4% dermal absorption based on LOAEL/NOAEL
2	Europe	217 µg/day	Aggregate exposure, three scenarios, 100% inhalation, 50% dermal absorption based on NOAEL
3	Australia	420 µg/day	Aggregate exposure from up to 10 products based on NOAEL
4	Japan	4.3 µg/day	Estimation of general population exposure using Monte Carlo simulation based on MOE of NOAELs
5	California	30 µg/day	Based on LCR 10^{-5}
6	SCCS	55 µg/day	Based on LCR 10^{-5}

3.2 Mechanism of Formation of 1,4-Dioxane Contaminants in Cosmetics

1,4 Dioxane contamination in cosmetics comes from the manufacturing by-products of cosmetic raw materials made through ethoxylation processes, such as ethylene glycol, polyethylene glycol, and ethoxylated surfactants (such as Sodium Laureth Sulphate, polysorbates or fatty alcohol ethoxylates) ((Hayes et al., 2022). Ethoxylated surfactants are widely found in personal care and household products, such as detergents, body cleansers, shampoos, dishwashing detergents, and toothpaste. The mechanism of 1,4-Dioxane contamination can be seen in Figure 2.

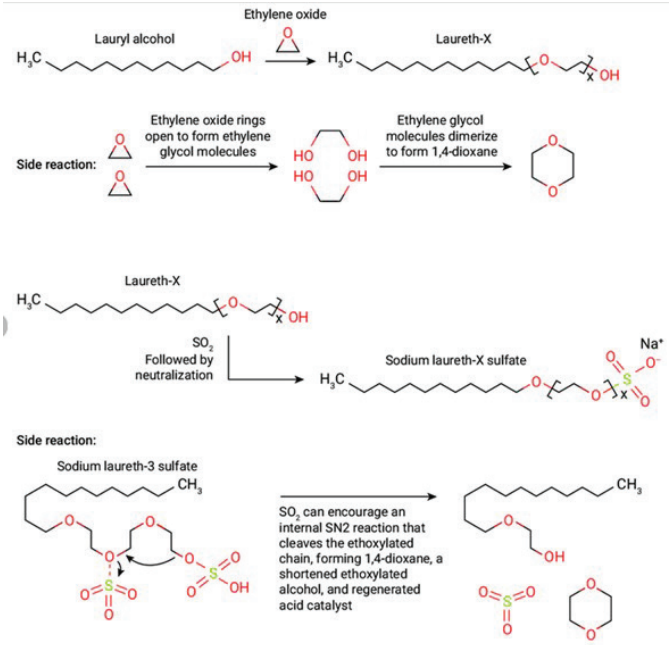

Figure 2. Ethoxylation Process Formation of By-Product 1,4-Dioxane (Ron Honnold et al., 2021)

3.3. International Regulation on 1,4-Dioxane

Several countries have established regulations related to 1,4-dioxane. Although 1,4-Dioxane has been banned from use as an ingredient in cosmetic products, 1,4-Dioxane is still allowed to be present as a contaminant at low levels, as summarized in Table 3 as follows:

Table 3. Regulation of 1,4-Dioxane in Various Countries

No.	Organization	Country	Exposure	Matrices	Results
1	Association of Southeast Asian Nations (ASEAN)	Brunei, Kamboja, Indonesia, Laos, Malaysia, Myanmar, Filipina, Singapore, Thailand and Vietnam	-	Cosmetic	NMT of 10 ppm
2	Food and Drug Administration (FDA)	United States of America	-	Cosmetic	Not yet set
3	Environmental Protection Agency (EPA)	United States of America	-	Drinking water	35 µg/L
4	The National Institute for Occupational Safety and Health (NIOSH)	United States of America	Workplace	-	One ppm; (3.6 mg/m3) upper boundary (30 minutes)
5	Occupational Safety and Health Administration (OSHA)	United States of America	Workplace	-	100 ppm, (360 mg/m3) 8-hour time-weighted average; Skin
5	Taiwan FDA	Chinese Taipei	-	Cosmetic	NMT of 100 ppm
6	European Medicine Agency (EMA)	Australia	-	Pharmacy	380 ppm

No.	Organization	Country	Exposure	Matrices	Results
7	Dutch Expert Committee on Occupational Safety	Netherlands	Workplace	-	20 mg/m3 (6 ppm)
8	Health Canada	Canada	-	-	Banned
9	Federal Department of Health	Australia			
10	Scientific Committee for Consumer Safety (SCCS)	European Union and England		Cosmetic	NMT of 10 ppm
11	Department of Environmental Conservation	The state of New York, United States of America		Cosmetic	NMT of 10 ppm
				Household cleaning and personal care products	Two ppm

*NMT = No more than

The U.S Environmental Protection Agency (EPA) has classified 1,4-dioxane as "possibly carcinogenic to humans" based on finding sufficient evidence of carcinogenicity in animals intentionally exposed to 1,4-Dioxane but insufficient evidence of carcinogenicity in humans. ((U.S. Food and Drug Administration (FDA), 2022). The U.S FDA has not set limits on the amount of dioxane allowed in cosmetics. Although it has not conducted an independent risk assessment, the FDA has periodically monitored dioxane levels in cosmetic products sold in the United States since the late 1970s. Following recommendations to implement changes in manufacturing processes to reduce these contaminants, the FDA has reported significantly reduced levels of dioxane in cosmetics over the years (Ramos, n.d.).

On the other hand, the state of New York, through New York Senate Bill No. S4389B, for the first time, set limits on dioxane in cosmetics, household cleaning products, and personal care due to concerns about the general public's exposure to dioxane through drinking water. This law limits dioxane levels to 10 ppm in cosmetics starting December 31st, 2022 (Ramos, n.d.). moreover, the European Commission, when preparing policies and proposals related to consumer safety, health, and the environment, relies on independent Scientific Committees to provide scientific advice. One is the European Commission Scientific Committee on Consumer Safety (SCCS). The SCCS thinks that levels of 1,4-Dioxane in cosmetic products of ≤10 ppm are considered safe for consumers (SCCS, 2015). Meanwhile, the Association of Southeast Asian Nations (ASEAN) has updated the Cosmetic Contaminant Limit Guidelines to Version 3.0. At the 30th ACSB Meeting held in Nay Pyi Taw, Myanmar, June 18th-19th, 2019, it was decided that from June 19th, 2020, cosmetic products in ASEAN countries should not contain more than 25 ppm of 1,4-Dioxane as a contaminant, and from June 19th, 2023, the limit is reduced to no more than ten ppm (ASEAN, 2019).

3.4 1,4-Dioxane Testing Capability of Indonesian FDA Laboratories in Indonesia

Since 2022, the Indonesian FDA has started implementing a laboratory regionalization pilot project to strengthen Indonesia's food and drug control system. The

Indonesian FDA Magazine Edition XII/2022 stated that laboratory regionalization is defined as a grouping of laboratories based on region and testing specialization to increase effectiveness and efficiency while prioritizing the validity and speed of testing to accelerate supervisory follow-up. There is a change in policy direction in the concept of laboratory regionalization in 2023, making it mandatory for all POM Centers/Branches to test all chemical testing parameters using gas chromatography-tandem mass spectrometry instruments. Throughout 2022, the supervision of the Agency in testing for 1,4-Dioxane contamination has been running quite well (Figure 3), where the Indonesian FDA provincial office in Palembang held the most significant number of testing samples for the 1,4-Dioxane parameter, while the smallest number of testing samples was held by the Indonesian FDA provincial office in Medan (Annual Report of Indonesian FDA Provincial Offices in Palembang and Medan in 2022).

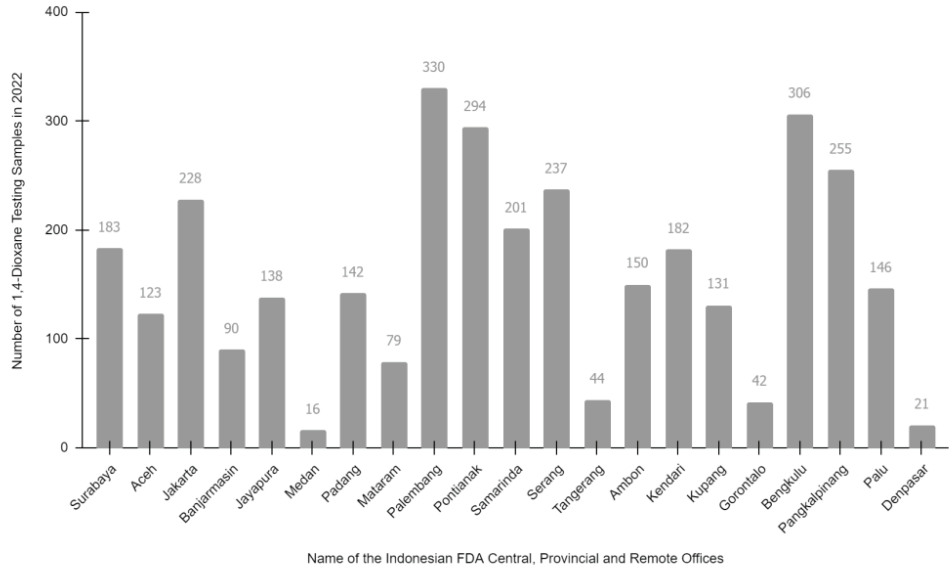

Figure 3. Testing Chart of 1,4-Dioxane Samples at The Indonesian FDA Central Office and Provincial Offices Across Indonesia

The planning and implementation of sampling and testing of traditional medicines, quasi medicines, health supplements, and cosmetics is stipulated by the deputy for supervision of traditional medicines, health supplements, and cosmetics, which is a reference for work units in carrying out sampling and testing of traditional medicines, quasi medicines, health supplements, and cosmetics. This guideline regulates product types and sample categories that must be tested for dioxane content, as shown in Table 4.

Table 4. Product Types and Categories of Cosmetics with 1,4-Dioxane Test Parameters

No.	Product Type	Category
1	Cream, emulsion, liquid, viscous liquid, gel, oil for skin (face, hands, feet, etc.)	Other baby preparations
2	Bath soap, antiseptic body wash, etc.	Baby bath soap, solid
		Hand soap, solid
		Bath soap, solid
3	Bath preparations (bath salts, foam, oils, gels, etc.)	Liquid body wash
		Hand wash soap (liquid)
		Bath foam
		Bath oil
		Bath salt
		Bath powder
		Other bathing preparations
		Baby bath soap, liquid
4	Hair Preparations	Shampoo
		Dry Shampoo
		Dandruff Shampoo
		Hair and body wash
		Baby hair and body wash
		Hair conditioner
		Hair Creambath
		Hair Mask
		Baby shampoo
		Other baby hair preparations
5	Oral and dental care preparations	Dentrifice
		Mouthwashes
		Mouth freshener

In this guideline, the cosmetics that should be tested for 1,4-Dioxane content contain ingredients made through the ethoxylation process. It should also be noted that cosmetics containing polyethylene glycol (PEG), polyethylene, polyoxyethylene, or oxynol may contain 1,4-Dioxane (Wilbur et al., 2012).

3.5 Development of 1,4-Dioxane Regulations in Indonesia

Regulations in Indonesia regarding 1,4-Dioxane yearly have developed based on the latest developments. Initially, 1,4-Dioxane was a prohibited ingredient in cosmetics according to the Regulation of the Head of the Food and Drug Administration of the Republic of Indonesia No. HK.00.05.42.1018 concerning Cosmetic Ingredients in 2008 Appendix I List of Prohibited Cosmetic Ingredients No. 476. This regulation is further amended into the Head of Food and Drug Administration Regulation No. 8/2015, 1,4-Dioxane is listed in Appendix V List of Prohibited Ingredients in Cosmetics No. 433. In the Food and Drug Administration Regulation No. 23 Year 2019 on Technical Requirements for Cosmetic Ingredients, 1,4-Dioxane is listed in Appendix V of the List of Unauthorized Ingredients in Cosmetics No. 433. In addition to the above regulations, 1,4-Dioxane is regulated in the Food and Drug Administration Regulation No. 12 Year 2019 on Contaminants in Cosmetics. 1,4-Dioxane is included as a contaminant, which is something that enters cosmetics unintentionally and unavoidably originating from processing, storage, and carried from raw materials. 1,4-Dioxane is a chemical contaminant from cosmetics containing ingredients made through ethoxylation processes, such as Sodium Laureth Sulphate or Polyethylene Glycol. In this regulation, the limit of 1,4-Dioxane is no more than 25 mg/kg or 25 mg/L (25 ppm). This regulation on cosmetic ingredients may undergo changes based on discussions at the ASEAN Cosmetic Scientific Body (ACSB) session, where it was agreed that the 1,4-Dioxane contamination limit would change to no more than 10 mg/kg or ten mg/L (10 ppm) and came into effect on June 19, 2023.

Table 5. Dioxane Regulatory Data and Analysis Methods CNQLDF

No.	Regulation	1,4-Dioxane Requirements	CNQLDF Analytical Methods	Results
1	Indonesian FDA Regulation No. Hk.00.05.42.1018/2018 about cosmetic ingredients	1,4-Dioxane as a Prohibited Cosmetic Ingredient Number 476	No. 12/KO/10	-
2	Indonesian FDA Regulation No.18/2015 about technical requirements for cosmetic ingredients	1,4-Dioxane as a Prohibited Ingredient in Cosmetics No. 433	No. 44/KO/MA-PPPOMN/18	LOD = 0,12 mg/kg
3	Indonesian FDA Regulation No. 23/2019 about technical requirements for cosmetic ingredients	1,4-Dioxane as an Unauthorized Ingredient in Cosmetics No. 433	-	-
4	Indonesian FDA Regulation No. 12/2019 about contaminants in cosmetics	1,4-Dioxane contamination limit not more than 25 mg/kg or 25 mg/L (25 bpj)	No. 22/KO/MA-PPPOMN/20	LOQ = 0,29 mg/kg
6	Discussion at the ASEAN Cosmetic Scientific Body meeting	Maximum 1,4-Dioxane requirement of 10 ppm as of June 19, 2023	No. 01 /KO/MA-PPPOMN/22	LOQ = 0,27 mg/kg

CNQLDF, in overseeing Regulations related to cosmetic ingredients, also made adjustments in the development of analytical method for testing 1,4-Dioxane. In 2010,

analytical method No. 12/KO/10 on the Identification of 1,4-Dioxane in cosmetic products by Gas Chromatography-Mass Spectroscopy was developed. Then it followed the updated one on No. 44/KO/MA-PPPOMN/18 with a shifted purpose, from identification to determination of levels in anticipation of changes in the regulation of 1,4-Dioxane as a contaminant that has a maximum limit, then refined by adding internal standard (IS) Tetrahydrofuran written in AM number 22/KO/MA-PPPOMN/20. Finally, this analytical method has been refined again by replacing the IS using the isotope of 1,4-Dioxane, 1,4-Dioxane-d8, with AM No. 01 /KO/MA-PPPOMN/22. This IS replacement regarded to feedback from several ASEAN members to create the ASEAN Cosmetic Method (ACM). The comparison between the applicable regulations and the developed AM as illustrated in Table 5.

3.6 Regional Harmonization of 1,4-Dioxane Methods

To strengthen the testing capabilities of 1,4-Dioxane, stakeholders need an analytical method that can be used for both pre and post-market surveillance. Indonesia, in this case, CNQLDF, was appointed as the leader in the development of 1,4-Dioxane AM for ASEAN (ASEAN Cosmetic Method, ACM). The process of establishing this ACM has gone through a long process, according to the ASEAN Guideline on Establishing the ASEAN Cosmetic Method (ACM). The establishment of ACM is carried out through several stages of activities, starting from identifying ASEAN member states (AMS) with related MAs, then comparing these AMs, and selecting the best AM, including the validation results. Indonesian AM have the best sensitivity, thus it was chosen due to Gas Chromatography Tandem Mass Spectrometry-Head Space (GCMS-HSS) has been selected as the preferred instrument to become ACM candidates. The next step was to refine the MA, in this case, making internal changes to the standards used, according to input from other AMS in the ACTLC meeting. AM revalidation was then carried out using the internal standard isotope of 1,4-Dioxane 1,4-Dioxane-d8. After the AM revalidation stage was carried out, the collaboration test of the AM was continued. Furthermore, a manuscript report was made along with a draft ACM. Input was sought from other AMS on the report manuscript and draft ACM, which were then finalized by adopting the AM into ACM.

The collaborative study conducted from August to September 2022. It was attended by 10 participants, consisting of three ASEAN member countries, namely the Philippines, Thailand, and Viet Nam, and seven laboratories in Indonesia, namely Indonesian FDA provincial offices in Padang, DKI Jakarta, Pontianak, Denpasar, Mataram, Pangkal Pinang and CNQLDF. The test objects were taken from products on the market and met the homogeneity and stability test requirements. The collaboration test results are sr=0.14393; sR=1.74388; RSDR=14.5010; PRSD=11.00388; HORRAT=1.318, or it can be concluded that the reproducibility of the method meets the requirements ($0.5 < \text{HORRAT} \leq 1.5$). The AM validation results for determining 1,4-Dioxane levels in cosmetic products using GCMS-HSS gave the following values (Table 6).

Table 6. 1,4-Dioxane Validation Parameter Value

No.	Validation Parameters	Acceptance Condition	GCMS Study
1	Selectivity	Resolution ≤ 1.5	Rt 1,4- Dioxane 8.816, Rt 1,4- Dioxane -d8 8.704 m/z 1,4-Dioksan 88, 58, 43 m/z 1,4- Dioxane -d8 96, 64, 46
2	Linearity	Vx0 ≤ 5.0	r = 1.000; Vx0 = 1.4%
3	Precision	RSD 12.5% (1.21 µg/g) ≤ 7,3	0,3%
		RSD 100% (10.28 µg/g) ≤ 7,3	1,1%
		RSD 125% (13.09 µg/g) ≤ 7,3	0,2%
4	Accuracy	% Recovery 12.5% (1.21 µg/g) = 80 – 110	94,6 – 95,7
		% Recovery 100% (10.28 µg/g) = 80-110	99,4 – 101,0
		% Recovery 125% (13.09 µg/g) = 80-110	101,7 – 102,1
5	LOD	-	0,08 µg/g
6	LOQ	-	0,27 µg/g

3.7 Harmonization of 1,4-Dioxane Method at the National Level

Through the notification system, the industry is fully responsible for the quality, safety, and benefits of the products produced. One of the efforts to strengthen pre-market supervision is to build cross-sectoral cooperation to strengthen industrial laboratories and external laboratories that carry out cosmetic testing.

To date, 15 external laboratories have their cosmetic testing performance accredited ISO 17025: 2017. Of these 15 laboratories, only two laboratories could carry out 1,4-Dioxane testing. Therefore, it is necessary to strengthen pre-market supervision by conducting cross-sector collaboration within the ICLN to equalize the ability of cosmetic testing among laboratories. Some of the collaboration steps taken were as follows:

a. Training on validation of analytical methods to equalize perception in carrying out AM validation
b. Technical training on cosmetic testing to improve personnel competency in conducting cosmetic testing or implementing new AM.
c. Implementation of proficiency test to assess laboratory performance
d. Organization of collaboration tests to assess the robustness of analytical methods
e. Development of the ICLN website as a forum for all members to exchange information about cosmetic testing
f. Harmonization of AM, both at the national, ASEAN regional, and international levels

Harmonization of analytical methods at the national, regional, and international levels is an effort to harmonize existing analytical methods so that all laboratories have the same reference standard for analytical methods when conducting sample testing. The objectives of standardization according to RI Law No. 20/2014 were as follows:

a. Improve quality assurance, production efficiency, national competitiveness, fair and transparent business competition in trade, business certainty, and the ability of business actors, as well as the ability of technological innovation.
b. Increasing protection to consumers, business actors, labor, and other communities, as well as the state, both from the aspects of safety, security, health, and preservation of environmental functions
c. Increase certainty, smoothness, and efficiency of trade transactions in goods and services domestically and abroad

Harmonization of cosmetic analysis methods at the national level is carried out through the issuance of Indonesian National Standards (INS). INS on Cosmetics can prevent disputes over test results and increase the competitiveness of the nation's products. The formulation of analytical methods into INS involves various stakeholders who are members of the Cosmetics Technical Committee, consisting of representatives from NQCLDF, Directorate of Standardization and Quality Control - Ministry of Trade, Center for Standardization and Services for the Chemical, Pharmaceutical and Packaging Industries - Ministry of Industry, Academic Experts from the University of Indonesia, PT Saraswati Indo Genetech, PT SGS Indonesia, PT Angler BioChemlab, Indonesian Cosmetics Association (Perkosmi), Indonesian Consumers Foundation (ICF).

To increase the capacity of 1,4-Dioxane testing in Indonesia, the Indonesian FDA needs to harmonize the analytical testing methods for 1,4-Dioxane contamination at the national level by issuing the Indonesian National Standards (INS). This ACM method is intended to be widely utilized by stakeholders and external laboratories for pre-market supervision of cosmetic products to ensure product quality and safety.

4. Conclusion

The analytical method for determining 1,4-Dioxane levels in cosmetics by GCMS-HSS developed by CNQLDF has been collaborated and harmonized at the regional level into ACM 011 and in the process of harmonization at the national level into INS. With the harmonization of this method, all cosmetics laboratories in Indonesia and ASEAN, including those incorporated in JLKI, have standardized analytical methods for testing 1,4 Dioxane to strengthen pre-market supervision of cosmetic products in ensuring product quality and safety.

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