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A Case Report of Contamination and Toxicity of Ethylene Glycol and Diethylene Glycol on Drugs in Indonesia

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Abstract Every individual has a right to access safe medicine. However, in fact, drug contamination still occurs in several countries. The Indonesian authorities through the Indonesian Food and Drug Supervisory Agency or *Badan Pengawas Obat dan Makanan* (BPOM) *Indonesia* declared five drug products contaminated with ethylene glycol (EG) and diethylene glycol (DEG) on October 19, 2022. The concentration of the chemicals exceeded 0.5 mg/kg body weight per day based on recognized pharmacopeia and BPOM Indonesia. Based on the pharmaceutical issues, this study aimed to disseminate information on drugs contaminated with EG and DEG in Indonesia along with their effects. The descriptive method with a case report approach was used in this study. Secondary data of previous research were obtained from the website of the Indonesian state authorities such as the Indonesian Ministry of Health, the Food and Drug Supervisory Agency, and some journal databases. Data collection was carried out from October 12 to December 22, 2022. A total of 323 cases of acute kidney injury and 190 deaths in children were reported by the Indonesian Ministry of Health. The investigation results show that contamination from EG and DEG as solvents was found in some drugs; as a result, the drugs did not meet the quality standards. A total of 103 syrup drugs contaminated had caused acute kidney injury and six companies that produced contaminated drugs were given several sanctions for their negligence.

Keywords Acute Kidney Injury, Indonesian Food and Drug Supervisory Agency, Diethylene Glycol, Ethylene Glycol, Syrup Drug

1. Introduction

Access to safe medicine means having health treatment free from biological, chemical, and physical contamination. However, drug contamination still occurs in several countries. A diethylene glycol contamination in paracetamol was reported in 1990 in Dhaka, Bangladesh [1]. Diethylene glycol was found in 19 paracetamol bottles, and the contamination was identified in seven of the 28 brands tested [1]. The residues of diethylene glycol were found in the drug brand "My Pikin" in 2008 in Nigeria, West Africa [2]. Several other countries also reported some cases related to diethylene glycol contamination in India, the United States, Haiti, and Panama causing an epidemic of diethylene glycol poisoning [3-7]. The Indonesian authorities through the Food and Drug Supervisory Agency or *Badan Pengawas Obat dan Makanan* (BPOM)

Indonesia recently declared five drug products contaminated with ethylene glycol with concentrations exceeding 0.5 mg/kg body weight per day based on recognized pharmacopoeia and national standards [8].

Ethylene glycol ($C_2H_6O_2$) and its derivatives such as diethylene glycol ($C_4H_{10}O_3$), methanol, ethylene glycol, and isopropyl alcohol are categorized as "toxic alcohol". Exposure to ethylene glycol (EG) and diethylene glycol (DEG) can be very dangerous and leads to high morbidity and mortality if not treated immediately [9-11]. EG and DEG are colorless and sweet liquids which are used for antifreeze. EG and DEG in the incorporate pharmaceutical act as a solvent. The exposure to EG and DEG occurs through the ingestion. Due to their colorless nature and sweet taste, EG and DEG pose a possible risk of accidental ingestion. Meanwhile, the chemicals can harm individuals if they are taken by those who attempt to suicide, get drunk without using ethanol, or misuse them for drug solvents [12-14]. Exposure to EG and DEG causes various toxicity levels to public health.

The American Association of Poison Control Centers released an annual report of the National Poison Data System in its 2016 about 6,347 cases of ethylene glycol poisoning [15]. The published data reveal that 686 of 6,347 cases occurred children under 12 years of age [15]. Similarly, the Indonesian Ministry of Health declared 323 acute kidney injury (AKI) cases in children aged 1-5 years and a total of 190 deaths [16]. The background becomes the basis for this current study to disseminate information on drugs contaminated with EG and DEG in Indonesia along with their toxic effects.

2. Materials and Methods

The descriptive method with a case report approach was used in this study. Secondary data were collected from the website of the Indonesian state authorities such as the Indonesian Ministry of Health and the Indonesian Food and Drug Supervisory Agency, as well as journal databases. Qualitative data in this study included brands of drugs contaminated with EG and DEG, while quantitative data included license number. Data collection was carried out from October 12 to December 22, 2022.

3. Result and Discussion

The data analysis results show that three pharmaceuticals contained propylene glycol and EG during production. The six pharmaceutical companies that used the chemicals were Yarindo Farmatama Inc., Universal Pharmaceutical Industries Inc., Afi Farma Inc., Ciubros Farma Inc., Samco Farma Inc., and Rama Emerald Multi Sukses Inc. Six products of Yarindo Farmatama Inc. were revoked from distribution. Universal Pharmaceutical Industries Inc. had 10 products which were stopped being distributed. This study found product permits revoked for 39 products from Afi Farma Inc., 6 products from Ciubros Farma Inc., 8 products from Samco Farma Inc., and 32 products from Rama Emerald Multi Sukses Inc.. The list of medicinal products with unpermitted distribution license is presented in Table 1.

Table 1. List of Medicinal Products whose Distribution Permits were Revoked because Contaminated EG and DEG 22 December 2022

Brand	License Number	Incorporated Pharmaceuticals
Cetirizine HCl	GKL1132716437A1	Yarindo Farmatama Inc.
Dopepsa	DKL1532719133A1	Yarindo Farmatama Inc.
Flurin DMP	DTL0332708637A1	Yarindo Farmatama Inc.
Sucralfate	GKL1532719233A1	Yarindo Farmatama Inc.
Tomaag Fortee	DBL0432709433A1	Yarindo Farmatama Inc.
Yarizine	DKL1132716237A1	Yarindo Farmatama Inc.
Antasida DOEN	GBL1926303433A1	Universal Pharmaceutical Industries Inc.
Fritillary & Almond Cough Mixture	DTL7826303137A1	Universal Pharmaceutical Industries Inc.
Glynasin	DTL8826303137A1	Universal Pharmaceutical Industries Inc.
New Mentasin	DTL7226302837A1	Universal Pharmaceutical Industries Inc.
Unibebi Cough Syrup	DTL7226303037A1	Universal Pharmaceutical Industries Inc.
Unibebi Cough Syrup (orange flavor)	DTL2026303537A1	Universal Pharmaceutical Industries Inc.
Unibebi Demam	DBL1926303336A1	Universal Pharmaceutical Industries Inc.
Unibebi Demam	DBL8726301237A1	Universal Pharmaceutical Industries Inc.
Unidryl	DTL0526302637A1	Universal Pharmaceutical Industries Inc.
Uniphenicol	DKL9626301133A1	Universal Pharmaceutical Industries Inc.
Univxon	DTL7226302937A1	Universal Pharmaceutical Industries Inc.

Table 1 continued

Uni OBH	DBL7226303237A1	Universal Pharmaceutical Industries Inc.
Afibramol	DBL1801707736A1	Afi Farma Inc.
Afibramol	DBL0801705537A1	Afi Farma Inc.
Afibramol grape flavor	DBL1801708037A1	Afi Farma Inc.
Afibramol apple flavor	DBL1801708237A1	Afi Farma Inc.
Afibramol orange flavor	DBL1801707837A1	Afi Farma Inc.
Afibramol 250	DBL1901705537C1	Afi Farma Inc.
Afibramol 160	DBL1901705537B1	Afi Farma Inc.
Aficitrin	DTL9101701037A1	Afi Farma Inc.
Ambroxol HCl	GKL1901709137A1	Afi Farma Inc.
Antasida DOEN	GBL1701707233A1	Afi Farma Inc.
Broncoxin	DTL2101710037A1	Afi Farma Inc.
Cetirizine Hydrochloride	GKL1801708731A1	Afi Farma Inc.
Chloramphenicol Palmitate	GKL2101710133A1	Afi Farma Inc.
Coldys Jr	DTL1701707133A1	Afi Farma Inc.
Coldy's Jr Forte	DTL1901707133B1	Afi Farma Inc.
Domino	DKL1901709636A1	Afi Farma Inc.
Domino	DKL1701707533A1	Afi Farma Inc.
Domperidone	GKL1901709536A1	Afi Farma Inc.
Domperidone	GKL1701707433A1	Afi Farma Inc.
Ecomycetin	GKL2101710233A1	Afi Farma Inc.
Fumadryl	DTL9601702937A1	Afi Farma Inc.
Gastricid	DBL1901709233A1	Afi Farma Inc.
Ibuprofen	GTL1701707033A1	Afi Farma Inc.
Ibuprofen	GTL1901707033B1	Afi Farma Inc.
Obat Batuk Hitam	GBL8701700435A1	Afi Farma Inc.
OBH Afi	DBL9401701737A1	Afi Farma Inc.
OBH Afi lemon flavor	DBL2001709737A1	Afi Farma Inc.
OBH Afi mint flavor	DBL2001709837A1	Afi Farma Inc.
Paracetamol	GBL1801707636A1	Afi Farma Inc.
Paracetamol grape flavor	GBL1801708137A1	Afi Farma Inc.
Paracetamol apple flavor	GBL1801708337A1	Afi Farma Inc.
Paracetamol orange flavor	GBL1801707937A1	Afi Farma Inc.
Paracetamol mint flavor	GBL0101704237A1	Afi Farma Inc.
Paracetamol strawberry flavor	GBL1701707337A1	Afi Farma Inc.
Resproxol	DKL2001709936A1	Afi Farma Inc.
Resproxol	DKL1901709037A1	Afi Farma Inc.
Vipcol	DTL7801706637A1	Afi Farma Inc.
Zinc Go	DTL1801708437A1	Afi Farma Inc.
Zinc Go Forte	DTL1801708437B1	Afi Farma Inc.
Zinc Sulfate Monohydrate	GTL1801708931A1	Afi Farma Inc.
Zyleron	DKL1801708837A1	Afi Farma Inc.
Citocetin	DTL7804005733A1	Ciubros Farma Inc.
Citomol	DBL9304003837A1	Ciubros Farma Inc.
Citophenicol	DKL8304002433A1	Ciubros Farma Inc.

Table 1 continued.

Citoprim	DKL9604004633A1	Ciubros Farma Inc.
Floradryl	DTL9504004437A1	Ciubros Farma Inc.
Popalex	DTL9904005537A1	Ciubros Farma Inc.
Costan	DKL2021908533A1	Samco Farma Inc.
Domestrium	DKL1521908133A1	Samco Farma Inc.
Samcodryl	DTL8821904637A1	Samco Farma Inc.
Samcodryl Expectorant	DTL9021905637A1	Samco Farma Inc.
Samconal	DBL8821905137A1	Samco Farma Inc.
Samconal	DBL0321907136A1	Samco Farma Inc.
Samtacid	DBL7821905333A1	Samco Farma Inc.
Toxaprim	DKL1521908033A1	Samco Farma Inc.
Ambroxol HCl	GKL1428912037A1	Rama Emerald Multi Sukses Inc.
Antasida DOEN	GBL9628907033A1	Rama Emerald Multi Sukses Inc.
Broxolic	DKL1428912137A1	Rama Emerald Multi Sukses Inc.
Calortusin	DTL8328910737A1	Rama Emerald Multi Sukses Inc.
Calortusin PE	DTL2028918937A1	Rama Emerald Multi Sukses Inc.
Cetirizine Hydrochloride	GKL1928916436A1	Rama Emerald Multi Sukses Inc.
Cetirizine Hydrochloride	GTL1628912937A1	Rama Emerald Multi Sukses Inc.
Cetirizine	DKL1928916336A1	Rama Emerald Multi Sukses Inc.
Cetirizine	DTL1628913037A1	Rama Emerald Multi Sukses Inc.
Cotrimoxazole	GKL1328911233A1	Rama Emerald Multi Sukses Inc.
Dolorstan	DKL1428912233A1	Rama Emerald Multi Sukses Inc.
Domperidone Maleate	GKL2028919036A1	Rama Emerald Multi Sukses Inc.
Domperidone Maleate	GKL2028919133A1	Rama Emerald Multi Sukses Inc.
Fenpro	DTL1428911933A1	Rama Emerald Multi Sukses Inc.
Ibuprofen	GTL1528912433A1	Rama Emerald Multi Sukses Inc.
Noze	DTL1828915236A1	Rama Emerald Multi Sukses Inc.
OBH Rama	DBL1228911137A1	Rama Emerald Multi Sukses Inc.
Paracetamol	GBL1828915536A1	Rama Emerald Multi Sukses Inc.
Paracetamol	GBL8528902637A1	Rama Emerald Multi Sukses Inc.
Pseudoephedrine HCl	GTL1828915436A1	Rama Emerald Multi Sukses Inc.
Ramadryl Atusin	DTL8328901137A1	Rama Emerald Multi Sukses Inc.
Ramadryl Expectorant	DBL8328900137A1	Rama Emerald Multi Sukses Inc.
Ramagesic	DBL1828915336A1	Rama Emerald Multi Sukses Inc.
Ramagesic	DBL8328900637A1	Rama Emerald Multi Sukses Inc.
Ratrim	DKL8328911733A1	Rama Emerald Multi Sukses Inc.
Remco Cough	DTL0428910937A1	Rama Emerald Multi Sukses Inc.
R-Zinc	DTL1928917537A1	Rama Emerald Multi Sukses Inc.
Sucralfate	GKL2028919233A1	Rama Emerald Multi Sukses Inc.
Tera F	DTL1928916237A1	Rama Emerald Multi Sukses Inc.
Tera - PE	DTL1928917937A1	Rama Emerald Multi Sukses Inc.
Zinc Sulfate Monohydrate	GTL2028918736A1	Rama Emerald Multi Sukses Inc.
Zinc Sulfate Monohydrate	GTL1928917437A1	Rama Emerald Multi Sukses Inc.

Source: BPOM [17–19]

Table 1 is the result of an investigation on contaminated drugs conducted by the Indonesian Food and Drug Supervisory Agency [17]. The six corporates had 103 contaminated products containing propylene glycol as a raw material and the final products containing EG contaminants over the threshold. Chemical samples taken from one of the supply chains of the three corporates, namely CV SC was tested in the laboratory. Ten samples of the propylene glycol were detected to contain EG of 4.69-99.09%, while two EG samples were not detected to have the same contaminant. Test results show that two samples of sorbitol solvent from the chain were detected to contain EG and DEG of 0.03-1.34%. The concentration of the contaminants was inversely proportional to the safe threshold value in which EG and DEG in propylene glycol need to be at less than 0.1%, while the safe threshold or tolerable daily intake (TDI) for EG and DEG contaminants in medicinal syrup should not exceed 0.5 mg/kg body weight per day. Propylene glycol is a product of alcohol derivatives such as EG and DEG. It has the same physical (shape and appearance) and chemical properties as EG and DEG. In addition, it can function as a solvent but has very different toxicity. EG and DEG have a more harmful effect than propylene glycol.

Ethylene glycol (EG) is easily absorbed in the digestive tract. The levels of EG and DEG exposures vary. Various effects arise due to exposure to EG and DEG toxicity, and they include motion sickness, accompanied by the potential for depression in the central nervous system [20], [21]. During that time, exposure to EG and DEG often causes an increase in the osmolar volume but not in the anion chamber or acidosis. When the concentration of EG and DEG is present in the production of metabolites, it will decrease the osmolar volume and increase the anion chamber accompanied by the development of metabolic acidosis. The half-life time EG metabolized ranges from 4-12 hours, during which time metabolic acidosis and anion chambers develop to the accumulation of glycolic acid [22, 23]. At this time interval, a patient will experience pain or depression in the central nervous system accompanied by excessive or deeper breathing. Because the heart beats more than 100 times per minute, hypertension can also occur. After 12 hours, his/her condition will change to nephrotoxicity, characterized by an increase in creatinine due to the deposition of calcium oxalate crystals in the proximal tubule. The formation of calcium oxalate can trigger hypocalcemia, placing the patient at risk for tetany, seizures, QT prolongation, and dysrhythmias. Within 12-18 hours, oliguria then develops. If this condition is not treated immediately, it will cause acute kidney injury in children [22, 24, 25].

The Indonesian Ministry of Health declared a new acute kidney injury (AKI) case with an unidentified cause. The number of acute kidney injury (AKI) cases reached 189 cases in children in August-September 18, 2022 [26]. It increased to 323 cases in children aged 1-5 years and a total death of 190 cases on November 3, 2022. The number was the same from December 2022 to January 2023. However, the Indonesian Ministry of Health reported one confirmed case and one suspected case of acute kidney injury in DKI Jakarta in February 2023, and one of the patients was reported died. New acute kidney injury cases, per February 5, 2023, were found as many as 326 patients with acute kidney injury. One suspect spread across 27 provinces of Indonesia. From the total, 116 patients were declared cured, while six patients are still undergoing treatment at Dr. Cipto Mangunkusumo National Center General Hospital Jakarta [27]. The case occurred because the child consumed Praxion brand drugs contaminated with EG and DEG. The group at risk of the contamination was children aged 6 months-18 years, but cases are dominated in children aged 1-5 years [28]. Symptoms that appear in children include diarrhea, nausea, vomiting, fever for 3-5 days, cough, runny nose, frequent drowsiness and less and less urine/urination, and even unable to urinate at all [26]. Another symptom is a change in the color of the urine (dark or brownish). If the color of the urine changes in addition to decreasing volume of urine and absence of urine for 6-8 hours (during the day), parents are asked to immediately take their child to the nearest health care facility for further treatment [26].

Acute kidney injury (AKI) was identified due to EG and DEG contamination in pediatric medicine on November 9. 2022. The Indonesian Food and Drug Supervisory Agency imposed sanctions on three pharmaceutical companies, namely Yarindo Farmatama Inc., Universal Pharmaceutical Industries Inc., and Afi Farma Inc. The three companies stopped producing medicinal syrup, and returned the approval letter of the distribution permit for all medicinal syrups. Moreover, they also withdrew and ensured that all drug syrups had been withdrawn from circulation including pharmaceutical wholesalers, pharmacies, drugstores, and other pharmaceutical service facilities. They also destroy all supplies (stock) of medicinal syrup at the Technical Implementation Unit (UPT) Officer of Indonesian Food and Drug Supervisory Agency by making minutes of extermination. They reported on the implementation of orders to stop production, recall and destroy drug syrup to the Indonesian Food and Drug Supervisory Agency [17].

Concerning the acute kidney injury case in February 2023, the Indonesian Food and Drug Supervisory Agency received information from the Indonesian Ministry of Health about a syrup suspected to cause the acute kidney injury cases. The Indonesian Food and Drug Supervisory Agency then took steps by investigating, tracing, taking, and testing samples, including inspection of production facilities. The agency had conducted tracing, sampling, and testing of syrup samples left over from the patient's medication; circulation with the same batch number as the sample consumed by the patient; the production site (retained samples) with the same batch number as the sample consumed by the patient; adjacent batches; sorbitol raw materials used in the production process; and other

syrup samples using raw materials with the same batch number (two different syrup products). All the syrup and raw material samples were sent and tested at the laboratory of the Food and Drug Testing Development Center or *Pusat Pengembangan Pengujian Obat dan Makanan Nasional* (PPPOMN) of the Indonesian Food and Drug Supervisory Agency. The test results show that all samples tested were qualified (MS), meaning that the syrup met the daily safe intake threshold [29].

4. Conclusions

A total of 323 cases of acute kidney injury (AKI) and 190 deaths were reported by the Indonesian Ministry of Health. The investigation results from the Indonesian Food and Drug Supervisory Agency found EG and DEG contamination in the drug exceeding the quality standards. The use of EG and DEG as solvents leads to contamination in 103 syrup drugs. Six companies that produce contaminated drugs were given several sanctions for their negligence. It is necessary to tighten supervision carried out by the Indonesian Food and Drug Supervisory Agency and avoid similar cases in the future.

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