


BUKTI KORESPONDENSI


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Manuscript Information	
Manuscript ID:	14031059
Manuscript Title:	A Case Report of Contamination and Toxicity Ethylene Glycol and Diethylene Glycol on Drugs in Indonesia
Evaluation Report	
General Comments	The manuscript should be rewritten. The level of sentences and the structures are not to the mark. The authors might want to take help of professional proofreaders or colleagues who has expertise in writing for English journals. Repeatedly misused the acronyms throughout the text. This makes reading the manuscript cringeworthy. The level of written English needs to be alleviated. The sentence should have a kind of "sync" among them.
Advantage & Disadvantage	Advantage: Thorough investigation of the contaminated medications. The big table could have been included in the supplementary material (if it is permitted by the journal. Ask the editor, please). While, a smaller table with names of the companies, number of products/drugs that have been revoked and type of contamination (EG or DEG) would have much sense.
How to improve	The title should be rewritten with proper preposition - A case report of ... toxicity of ethylene glycol ... Page 1: In the abstract the second -Ministry of Health and the Food and Drug Administration (BPOM) - should be replaced by 'BPOM', while in the third case BPOM Indonesia could have been written as just BPOM. No need for repeated information. remove 'that' - "Safe medicine means it is free ...". Remove uppercased diethylene and

	<p>ethylene from the entire text. It is a common noun.</p> <p>EG and DEG should have been introduced at the first instance and not in the second paragraph.</p> <p>Page 2:</p> <p>Rewrite the sentence: "In line also ... 190m cases".</p> <p>Materials and Methods</p> <p>Use BPOM, instead of long names where applicable.</p> <p>Page 5:</p> <p>Again, use only BPOM, instead of the full name. Otherwise what is the need for including acronym when you do not use?</p> <p>Just EG not Ethylene glycol (EG).</p> <p>In the 2nd paragraph the effect of EG and DEG on central nervous system have been mentioned twice in the same paragraph. Rewrite the paragraph and take out repeated information.</p> <p>Again, just AKI and not acute kidney injury (AKI). Follow the citation style for multiple references.</p> <p>Page 6:</p> <p>"withdrawn and ensure that all drug syrups have been withdrawn " - These are example of bad sentence construction.</p> <p>Conclusions</p> <p>What do you mean by "Plenty of 323 cases"? Rewrite the conclusion section with proper scientific wordings.</p>
Please rate the following: (1 = Excellent) (2 = Good) (3 = Fair) (4 = Poor)	
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A Case Report of Contamination and Toxicity Ethylene Glycol and Diethylene Glycol on Drugs in Indonesia

Abstract ~~The~~Every individual has a right to ~~Access~~access to safe ~~medicine~~medicine is a right that must be fulfilled by the global community. ~~However~~However, in fact, drug contamination still occurs in several countries. ~~Recently, on 19 October 2022,~~ The Indonesian authorities through the ~~Indonesian~~ Indonesian Food and Drug Supervisory Agency or ~~Badan Pengawas Obat dan Makanan~~ (BPOM) ~~Indonesia~~ Indonesia declared ~~5-five~~ five drug products contaminated with ~~Ethylene-ethylene~~ ethylene glycol (EG) and ~~Diethylene-diethylene~~ diethylene glycol (DEG) on October 19, 2022. ~~The concentration of the chemicals exceeded with concentrations exceeding~~ 0.5 mg/kg body weight per day based on recognized pharmacopeia and national. Based on the ~~pharmaceutical issues~~ problems, this study ~~aim~~aimed to disseminate information on drugs contaminated with EG and DEG in Indonesia along with their ~~toxic~~ effects they cause. The descriptive method with a case report approach ~~was~~ used in this study. ~~This study uses~~ secondary data of ~~previous research~~ were obtained from the website of the Indonesian state authorities ~~such as the Indonesian Ministry of Health,~~ and the ~~Food and Drug Supervisory Agency~~ Food and Drug Administration (BPOM) ~~Indonesia, and some journal databases to deepen the study using a journal database.~~ Data collection was carried out from ~~12~~ October 12 to ~~22~~ December 22, 2022. A total of 323 cases of acute kidney injury (AKI) ~~in children and~~ with a total of 190 deaths ~~in children~~ were reported by the ~~Indonesian~~ Indonesian authorities through the Ministry of Health. The investigation results ~~from the BPOM Indonesia found~~ show that contamination from EG and DEG ~~contamination as solvents was found in the some drugs; as a result, the drugs did not meet that exceeded~~ the quality standards. ~~The use of EG and DEG as solvents is a cause of contamination.~~ A total of 103 ~~product~~ syrup drugs ~~were contaminated~~ ~~ensuing~~ had caused acute kidney injury AKI and the six incorporate that produced.

Keywords: ~~Acute~~ kidney injury, ~~Indonesian Food and Drug Supervisory Agency~~ BPOM, diethylene glycol, ethylene glycol, syrup drug

1. Introduction

~~Access to safe~~ The access to safe ~~medicine~~medicine is a right that must be fulfilled by the global community. ~~Sub~~ medicine means ~~that it is having health treatment~~ free from biological, chemical, and physical contamination. ~~However~~However, in reality, ~~drug~~ drug contamination still occurs in several countries. ~~In 1990 in Dhaka, Bangladesh,~~ there was ~~a~~ report of a case of 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 ~~7-seven~~ of the 28 brands tested [1]. ~~In 2008 in Nigeria, West Africa,~~ The residues of ~~Diethylene-diethylene~~ glycol were found in the drug brand "My Pikin" ~~in 2008 in Nigeria, West Africa~~ [2]. Several other countries ~~that~~ also reported ~~some cases related to Diethylene-diethylene glycol contamination were in~~ India, the United States, Haiti, and Panama ~~causing~~ ~~which at that time caused an epidemic of Diethylene-diethylene glycol poisoning~~ [3]–[7]. ~~Most recently, on October 19, 2022, in Indonesia,~~ The Indonesian authorities through the ~~Food and Drug Supervisory Agency or Badan Pengawas Obat dan Makanan~~ (BPOM) ~~Indonesia recently~~ ~~Food and Drug Administration~~ (BPOM) ~~Indonesia~~ Indonesia declared ~~5-five~~ five drug products contaminated with ethylene glycol with concentrations exceeding 0.5 mg/kg body weight per day based on recognized ~~pharmacopoeia~~ ~~pharmacopeia~~ and national standards [8].

Ethylene glycol (C₂H₆O₂) and its derivatives ~~such as~~ diethylene glycol (C₄H₁₀O₃), methanol, ethylene glycol, and isopropyl alcohol are categorized ~~under as~~ "toxic alcohol". ~~The term "toxic alcohol" is because~~ exposure to ~~Ethylene ethylene glycol (EG) and Diethylene-diethylene glycol (DEG) can be very dangerous with and leads to high morbidity and mortality if not treated immediately~~ [9]–[11]. EG and DEG are ~~in the form of colorless and sweet liquids, have a sweet taste, and which are used for antifreeze. Another use of EG and DEG in the incorporate~~ ~~is act~~ as a solvent. ~~The route of exposure entry for to~~ EG and DEG ~~exposure is occurs through the~~ ~~through~~ ingestion. Due to their colorless nature and sweet taste, EG and DEG pose a possible risk of accidental ingestion. Meanwhile, ~~intentional exposure~~ ~~the chemicals can harm individuals id can be in the form of they are taken by those who attempt~~ ~~toed~~ suicide, ~~desire to get drunk without using ethanol, or misuse of EG and DEG them by persons in the pharmaceutical incorporate~~ for drug solvents [12]–[14]. Exposure to EG and DEG ~~has causes varied 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 ~~annual report~~ ~~declared that there were~~ about 6,347 cases of ethylene glycol poisoning [15]. ~~Plenty of The~~

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Commented [A1]: There is a missing word after national. Since national is an adjective, you should follow it with a noun.

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and dysrhythmias. ~~In a time interval of~~ Within 12-18 hours, oliguria ~~then~~ develops. If this condition is not treated immediately, it will cause acute kidney injury ~~as occurs~~ in children in Indonesia [22], [24], [25].

Indonesian authorities through the ~~The Indonesian~~ Ministry of Health declared a new ~~case report of~~ acute kidney injury (AKI) ~~case with an unidentified cause. On August 18 September 2022, reports~~ The number of cases of acute kidney injury (AKI) ~~cases~~ reached 189 cases in children ~~in August-September 18, 2022~~ [26]. ~~On 3 November 2022 declared cases of~~ Acute Kidney Injury (AKI) ~~It increased to 323 cases in children aged 1-5 years as many as 323 cases with and a total death of 190 cases on November 3, 2022, December 2022 to January 2023. The number was the same in , there were a~~ December 2022 to January 2023 ~~additional cases of acute kidney injury.~~ However, in February 2023, the ~~Indonesian~~ Ministry of Health of the Republic of Indonesia reported one confirmed case and one suspected case of acute kidney injury in DKI Jakarta in February 2023, and one of ~~them the patients died was a reported death in February 2023. The reporting of additional a~~ New GGAPA cases, ~~until per~~ February 5, 2023, there were found as many as 326 patients with ~~cases of acute kidney injury (AKI) cases and one~~ One suspect spread across 27 provinces in of Indonesia. ~~Of these~~ From the total, 116 ~~cases~~ patients were declared cured, while six ~~cases~~ patients are still undergoing treatment at RSCM Jakarta [27]. The case occurred because the child consumed Praxion brand drugs contaminated with EG and DEG. The ~~risk group occurs at risk of the contamination was~~ in 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 ~~to water out for~~ is a change in the color of the urine (dark or brownish). If the color of the urine changes ~~and in addition to decreasing the volume of urine decreases, even if there is~~ and absence of ~~no~~ 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].

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

Concerning the GGAPA case in February, 2023, the ~~Indonesian Food and Drug Supervisory Agency Indonesian Food and Drug Administration (BPOM)~~ received information from the ~~Indonesian~~ Ministry of Health on February 2, 2023, about a syrup suspected to be the cause of ~~cause~~ the acute kidney injury cases. The ~~Indonesian Food and Drug Supervisory Agency Indonesian Food and Drug Administration (BPOM)~~ then took ~~responsive~~ steps by investigating, tracing, taking, and testing samples, including inspection of production facilities. The ~~Indonesian Food and Drug Supervisory Agency Indonesian Food and Drug Administration (BPOM) agency~~ has had conducted tracing, sampling, and testing of ~~samples on February 2-3, 2023 as follows:~~ syrup samples left over from the patient's medication; ~~syrup samples from~~ circulation with the same batch number as the sample consumed by the patient; ~~syrup samples from~~ the production site (retained samples) with the same batch number as the sample consumed by the patient; ~~syrup samples with~~ adjacent batches; sorbitol raw materials ~~samples~~ used in the production process; and other syrup samples using raw materials with the same batch number (~~2 two~~ different syrup products). All ~~the~~ syrup and raw material samples ~~mentioned above~~ were sent and tested at the laboratory of the ~~National Food and Drug Administration's (BPOMN)~~ Food and Drug Testing Development Center ~~or Pusat Pengembangan Pengujian Obat dan Makanan Nasional (PPOMN) in Indonesia~~ of the ~~Indonesian Food and Drug Supervisory Agency~~. The test results showed that all samples tested were qualified (MS), meaning that the syrup meets the daily ~~safe~~ intake threshold requirements, making it safe to use as long as it is following the ~~rules of use~~. [29]

4. Conclusions

Plenty of ~~Numbering to~~ 323 ~~cases of~~ acute kidney injury (AKI) ~~cases in children with~~ a total of 190 deaths were reported by the ~~Indonesian authorities through the Indonesian~~ Ministry of Health. The investigation results from the ~~Indonesian Food and Drug Supervisory Agency Food and Drug Administration (BPOM) Indonesia~~ found EG and DEG contamination in the drug that exceeded the quality standards. The use of EG and DEG as solvents is a cause of ~~leads to~~ contamination in ~~Heaps of~~ 103 syrup drugs, ~~were contaminated and the six incorporate~~ Six companies that

Commented [A7]: Please mention what it stands for.

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published data reveal that 686 of 6,347 cases occurred in children under 12 years of age [15]. In-line also occurred in Indonesia. Similarly, Indonesian authorities through the Indonesian Ministry of Health, 3 November 2022 declared cases of 323 acute kidney injury (AKI) cases in children aged 1-5 years and as many as 323 cases with a total death of 190 cases-deaths [16]. Based on these problems, the background becomes the basis for this current study to, this study aims to disseminate information on drugs contaminated with EG and DEG in Indonesia along with their toxic effects they cause.

2. Materials and Methods

The descriptive method with a case report approach is used in this study. This study uses Secondary data were obtained/collected from the website of the Indonesian state authorities such as the Indonesian Ministry of Health and the Food and Drug Administration (BPOM)-Indonesian Food and Drug Supervisory Agency, as well as to deepen the study using a journal database. Qualitative data in this study included brands and types of drugs contaminated with EG and DEG, while quantitative data included drug size. Data collection was carried out from 12 October 2022 to 22 December 2022.

3. Result and Discussion

The data analysis results of data collection and analysis show that three incorporated pharmaceuticals use contaminated Propylene glycol and EG in their production activities. The six incorporated 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. There were six products of Yarindo Farmatama Inc., whose distribution permits were revoked from distribution. Universal Pharmaceutical Industries Inc., for had 10 products whose distribution licenses were which were revoked/stopped being distributed. This study found product permits revoked for 39 products from Afi Farma Inc., for 39 products, 6 products from Ciubros Farma Inc., for 6 products, 3 products from Samco Farma Inc., for 3 products, and 32 products from Rama Emerald Multi Sukses Inc., for 32 products whose distribution licenses were revoked. The list of medicinal products whose with unpermitted distribution license has been revoked is presented in Table 1 below.

Table 1 is the result of an investigation on contaminated drugs conducted by the Indonesian Food and Drug Supervisory Agency Food and Drug Administration (BPOM)-Indonesia [17]. Six The six corporates incorporated and had 103 contaminated of its products were found to contain propylene glycol as a raw material and the contaminated finished final products contained by containing EG contaminants that exceeded over the safe limit threshold. Based on chemical samples in taken from one of the supply chains of the three incorporated corporates, namely CV SC which has been was tested in the laboratory, the ten results showed that as many as 10 samples of the raw material propylene glycol solvent sampled were detected to contain EG of 4.69-99.09%, while two samples EG samples were not detected to have the same contaminant. Test results on show that two samples of sorbitol-sorbitol solvent which were also sampled at the site from the chain were detected to contain EG and DEG of 0.03-1.34%. This finding is certainly. The concentration of the contaminants was inversely proportional to the safe threshold value for in which EG and DEG contamination in propylene glycol which has been seen needs to be at less than 0.1%, while the safe threshold or tolerable daily intake (TDI) for EG and DEG contamination-contaminants in medicinal syrup does not exceed/should not exceed 0.5 mg/kg body weight per day. Propylene Glycol glycol is a product of alcohol derivatives such as EG and DEG. Propylene Glycol 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) has properties that are easily absorbed in the digestive tract. The levels of EG and DEG exposures vary in severity. Various effects arise due to exposure to EG and DEG toxicity, for example and they include, such as motion sickness, accompanied by the potential for depression in the central nervous system depression [20], [21]. During that time, exposure to EG and DEG often cause an increase in the osmolar volume without an increase but not in the anion chamber or acidosis. When the concentration of EG and DEG is present in the production of metabolites, it will cause a decrease/increase the osmolar volume, and an increase in the anion chamber is accompanied by the development of metabolic acidosis. The half-life/half-life of EG metabolized ranges from 4-12 hours, during which time metabolic acidosis and anion chambers develop secondary to the accumulation of glycolic acid [22], [23]. At this time interval, the patient will experience pain or depression in the central nervous system pain or depression accompanied by excessive or deeper breathing. Because besides that the condition of the heart beats more than 100 times per minute, and hypertension can also occur. After a period of 12 hours, the 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,

Commented [A5]: What do you mean by half-life?

Commented [A6]: What do you mean by develop secondary here?

~~that produce contaminated drugs d-them~~ were given several sanctions for their negligence. It is necessary to tighten supervision carried out by the ~~Indonesian Food and Drug Supervisory Agency BPOM so that~~ and avoid similar cases ~~this case does not happen again in Indonesia~~ in the future.

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Contributor (s): Elanda Fikri, Yura Witsqa Firmansyah

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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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