



REVIEW ARTICLE

Challenges in utilizing diethylene glycol and ethylene glycol as excipient: A thorough overview

Mayank Baranwal, Ashmeen Kaur, Ranjeet Kumar

Department of Pharmacy Practice, ISF College of Pharmacy, Moga, Punjab, India

ABSTRACT

Diethylene glycol (DEG) and ethylene glycol (EG) are widely used excipients in pharmaceutical formulations, such as oral and topical preparations, due to their unique physical and chemical properties. However, the use of these glycols as excipients has been associated with numerous challenges, including their potential toxicity and regulatory concerns. The challenges associated with the use of DEG and EG as excipients, including their physicochemical properties, toxicity concerns, and regulatory requirements. It discusses the toxicological properties of DEG and EG including their mechanism of toxicity. It also highlights the regulatory guidelines governing the use of these excipients in pharmaceuticals and the measures that can be taken to mitigate the risks associated with their use. Overall, it aims to provide a comprehensive understanding of the challenges in utilizing DEG and EG as excipients and emphasizes the need for appropriate risk to patient.

KEY WORDS: Acute renal failure, Central Drugs Standard Control Organization, Diethylene glycol, Ethylene glycol, World Health Organization

INTRODUCTION

A medical product alert was given by the World Health Organization (WHO) on October 5, 2022 concerning four sub-standard, contaminated cough syrups identified in the country of Gambia, Africa region.^[1] A sub-standard medical product is that which does not meet quality standards or specifications. The four cough syrups that have been declared as contaminated by WHO are Kofexmalin Baby Cough Syrup, Promethazine oral solution, Magrip N Cold Syrup, and Makoff Baby Cough Syrup. The manufacturer of these products is Maiden Pharmaceuticals Limited (Haryana, India). The WHO declared manufacturers responsible for not assuring the safety and quality of these products. Impurities of diethylene glycol (DEG) and ethylene glycol (EG) were found in these four cough syrups by the WHO through laboratory analysis. So far, these four products have been identified in the Gambia, but may be distributed to other countries and regions through unofficial markets.^[2]

Address for Correspondence:

Mayank Baranwal,
E-mail: mbaranwal524@gmail.com

This alcohol is described in the scientific literature as a substance that can cause nephrotoxicity. Poisoning leads to severe metabolic acidosis with increased anion gap and acute kidney injury (AKI).^[3] DEG is an odorless, sweet substance that is toxic to humans.^[4] As an alcohol with special physicochemical properties, it has several uses in industry.^[5] DEG is a solvent found in many consumer goods such as antifreeze, brake fluid, lubricants, cosmetic creams, and paints.^[6]

EG is colorless and odorless and has a sweet taste. It is being used in industries, automobile coolants, heat transfer fluids, and runway deicers. It can be ingested as a cheap substitute for alcohol but have a risk of intoxication. Studies show that EG has been taken in an attempt to commit suicide. Its higher amount of ingestion causes metabolic acidosis

Access this article online

Website:

<http://isfcppharmaspire.com>

DOI:

10.56933/Pharmaspire.2023.15102

Date of Submission: 04 April 2023

Date of Revision: 20 April 2023

Date of Acceptance: 21 April 2023

and organ dysfunction. The mortality of EG intoxication is variable, ranging from 1% to 22%.^[7]

ROLE OF DEG AND EG AS EXCIPIENTS IN INDUSTRIAL FORMULATIONS

The global DEG market is projected to grow from 2.6 million metric tons in 2020–3.44 million metric tons by 2026 at a CAGR of 4.8%. The Asia Pacific region is expected to witness significant growth due to rising government investments in infrastructure development and rapid industrialization, particularly in India and China. DEG has various uses, including as a raw material for polyester resins and plasticizers, a humectant, dehydrating agent in natural gas, plasticizer for paper, and as demulsifier and lubricant as shown in Figure 1. The market is segmented by application, including antifreeze and coolant, solvents, humectants, polyester resins and plasticizers, emulsifiers and lubricants, and others, and by end-use industry, including agrochemical, automotive, cosmetic and personal care, paints and coatings, oil and gas, textiles, plastics industry, and others. The market growth is being driven by the growing demand for plasticizers in the plastics industry, as well as its extensive use in personal care and cosmetics products.^[8] The global DEG market is projected to grow at a CAGR of 4.8% from USD 163.79 Billion in 2022 to USD 400.43 Billion by 2030. DEG is a colorless, low viscosity liquid that dissolves fully in water, alcohol, organic solvents, and acetone. It is used as a solvent in industries such as textiles, printing, and paint pigments. It is also used as a raw material in the production of products such as polyester resins, thermoplastic polyurethanes, and plasticizers. The market's growth drivers include increased demand for cement and paints, while the toxic nature of DEG and patent registrations pose a restraint to its growth. The Asia-Pacific region holds the largest market share due to the increasing demand for various end-user industries such as building and construction, chemicals, and the automotive industry.^[9]

EG is a crucial reagent in the chemical industry, with applications in polymer production, antifreeze, brake

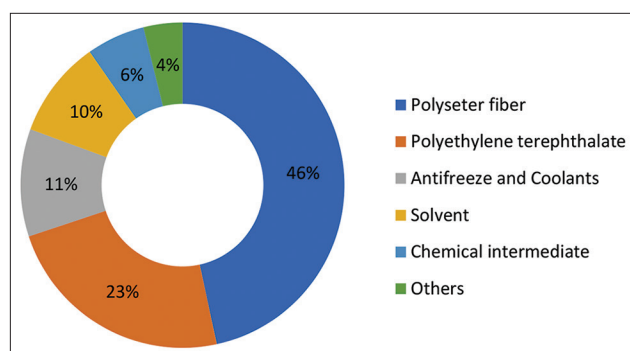


Figure 1: Application of diethylene glycol along with the proportions.

fluids, and anti-icing additives as depicted in Figure 2. The production and consumption of EG are growing, and there is a need for the purification and concentration of waste EG for reuse. Traditional methods for EG treatment, such as distillation, are energy-intensive and may require toxic reagents. Pervaporation, an environmentally friendly membrane technology, offers great potential for obtaining high-purity EG. There are three types of membranes, that is, inorganic, organic, and mixed matrix (MMM) membranes, which are produced from various membrane materials. This paper provides an overview of the current research and advances in pervaporation of EG mixtures, as well as a detailed analysis of dense polymer membranes, thin-film composites, and mixed matrix materials.^[10]

EPIDEMIOLOGY

The first and most notorious mass poisoning was of sulfanilamide contaminated with DEG termed as the Massengill disaster in America in 1937. DEG (72%, v/v) was used as solvent in the sulfanilamide elixir. No toxicity tests were performed on either the pre-marketing ingredients or the final products. Shortly thereafter, it was distributed in the United States. Mainly, the products were distributed in the southern states, where adverse effects and deaths were recorded. A total of 353 patients were hospitalized and 105 out of these patients died (34 children and 71 adults). This disaster led to formation of the United States Federal Food, Drug, and Cosmetic Act of 1938 which must approve the quality of drug product safety before selling.^[11] In 1969, seven children died of renal failure after taking over-the-counter sedatives (Pronap or Plaxim) in cape town, South Africa due to compromised quality.^[12] In 1985, five patients were treated in a Spanish burn ward where they developed anuria. Subsequent investigation showed that all patients were treated with topical silver sulfadiazine ointment however the patients died of renal failure despite continued care. The reason was due to 6.2–7.1 g/kg DEG contamination in the ointments. DEG is hardly absorbed in its normal form. Suspected skin and systemic toxicity were due to the combination of the wide range of treatments, repeated use of the product and the damaged skin of the patients.^[13]

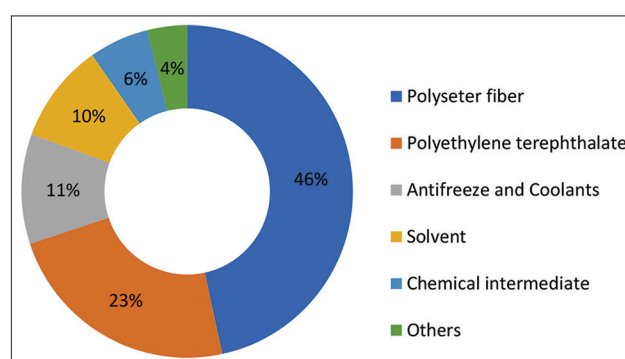


Figure 2: Application of ethylene glycol with proportions.

Twenty-one patients (from two separate incidents) died of renal failure in India after administering industrial glycerin (18.5%, v/v, containing DEG) as part of their treatment.^[11] In summer of 1990, 47 children were admitted to Jos University Teaching Hospital Nigeria, who later developed kidney failure and lost their lives. All were given paracetamol (acetaminophen) syrup contaminated with DEG which was used to replace propylene glycol.^[14] A similar case where 236 children died from this painkiller contamination was seen in Dhaka, Bangladesh between 1990 and 1992 [Table 1].^[15]

In Argentina around 1992, 29 people died of Propolis syrup contamination, and only found that the amount of DEG in it ranged from 24.00% to 66.5%. In 1996 in Port-au-Prince, Haiti, 88 of the many young infants were confirmed dead as a result of contaminated paracetamol. In 1998, 36 children developed acute renal failure after the intake of a cough expectorant manufactured in Gurgaon, India, and 33 of those children died despite receiving peritoneal dialysis and supportive care. Epidemiological investigations found that the drug contained 17.5% contamination of DEG. In Panama in 2006, there was an official estimate of 78 deaths and these resulted from unexplained renal failure with neurological dysfunction. Later, it was discovered that it was a cough syrup which was contaminated with an average of 8.1% DEG. The syrup was manufactured from glycerin imported from China through a European broker and the resulted cough syrup was found to be contaminated with an average of 22.2% DEGs. In the same year that meant another outbreak in China near 2006, 12 patients died from administration of contaminated armillarisin. In 2008, 84 children died in the country of Nigeria between November and December after ingesting a teething syrup contaminated with DEG. DEG was added to give a sweet

taste to Austrian wines. Consumption of this alcohol caused acute renal failure. 41 fake Sensodyne brand toothpastes found in the United Kingdom contaminated with DEGs were found in some other countries also, but no serious illness was reported from the use of these adulterated toothpastes.^[11]

In 2019–2020, some people in the Brazil, Belo Horizonte city from a small upscale brewery, drank a brand of beer containing an amount of DEG that initially caused symptoms such as, acute kidney failure, vomiting, abdominal pain, and blurred vision. Later, temporary blindness began to occur and fatalities were reported from this tragedy. The police found that the beer caused the deaths due to its contamination with diethyl glycol and its high concentration. In the first week of 2020, about 17 children were admitted to a hospital in Ramnagar, Jammu and Kashmir, India, who took Coldbest PC cough syrup as medicine and a batch of this cough syrup contained 34.97% of DEG. More than half of these children died of kidney failure. In October 2022, the WHO issued a medical product alert for four “contaminated” Indian pediatric drugs manufactured by Maiden Pharma in Sonipat, Haryana, India. The WHO stated that unacceptable amounts of DEG and EG have been found to be contaminated. The samples of each of the four products were confirmed by laboratory analysis by the WHO.^[16] In Gambia 66 children died, later the death increased to.^[1]

TOXICITY

EG

EG when enters the human body gets metabolized by an enzyme, alcohol dehydrogenase to form intermediary

Table 1: Tabular summary of events so far due to exposure to pharmaceutical medicine contaminated with diethylene glycol overdose

Country	Year	Contaminated product	How many deaths were reported?	References
USA	1937	Sulfanilamide	105	8
South Africa	1969	Sedative (Pronap or Plaxim)	7	9
Spain	1985	Silver Sulfadiazine	5	10
India	1986	Glycerine	21	8
Nigeria	1990	Paracetamol	47	11
Bangladesh	1990–1992	Paracetamol	236	12
Argentina	1992	Propolis syrup	29	8
Haiti	1996	Paracetamol	88	8
India	1998	Cough expectorant	33	8
Panama	2006	Cough syrup	78	8
China	2006	Armillarisin-A	12	8
Nigeria	2008	Teething syrup	84	8
Brazil	2019–2020	Beer	About 10	13
India	2020	Coldbest PC cough syrup	About 9	13
Gambia	2022	Cough syrup	About 70	1

products glycolic and oxalic acids. Glycolic acid causes metabolic acidosis whereas glycolate inhibits cellular respiration. In some patients, the metabolism of EG was observed to contribute to the development of lactic acidosis. Calcium oxalate, resulting from oxalic acid and calcium, may cause acute renal failure, neurological function, myocardial dysfunction, and pulmonary dysfunction. Deposition of calcium oxalate in tissues also causes hypocalcaemia, which suppresses cardiac function and BP [Figure 3].^[17]

DEG

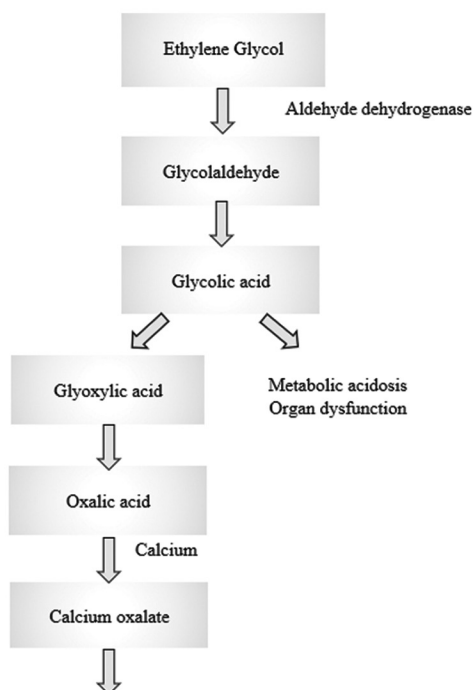
Pharmacokinetic data of DEGs were not obtained directly from humans, because of the high toxicity of DEG metabolites and furthermore, the diagnosis of this intoxication is usually delayed, which can make data collection and diagnosis difficult. Although two linked EG molecules occur in DEG, its metabolism produces different products, which are not EG and its by-products. Calcium oxalate crystals, one of the metabolites of EG, observed to be responsible for kidney injury. DEG is rapidly absorbed by the gastrointestinal tract when it is ingested orally and then is subsequently, widely distributed to most tissues via the bloodstream. According to an experimental study in primates, the peak of serum DEG concentration occurs between 30 and 60 min.^[3] DEGs have been implicated in large-scale poisonings worldwide due to accidental ingestion of contaminated drugs or fluids. Typical clinical signs of human DEG toxicity are AKI and a peripheral neuropathy characterized by reduced reflexes and

coordination of movement, weakness in the arms, legs, and face. DEG is metabolized to 2-hydroxyethoxyacetaldehyde, 2-hydroxyethoxyacetic acid (2-HEAA) and then to di-glycolic acid (DGA) with the help of alcohol dehydrogenase enzyme. HEAA is the main metabolite in the blood and urine and is responsible for metabolic acidosis. However, unlike the parent compound or other metabolites, DGA accumulates in the kidney and produces proximal tubule cell necrosis at toxic doses of DEG. DGA accumulation has been shown to be a nephrotoxic agent in DEG poisoning. The mechanism of neurotoxicity of DEGs was not fully understood till a recent study revealed development of neurotoxicity male rats.^[17] Animals that developed renal damage had significantly increased levels of DGA in the kidney compared to controls and animals that did not develop renal damage ($P < 0.05$). Renal DGA levels in animals with renal impairment averaged 9.6 mmol/g, while those without renal impairment averaged 0.9 mmol/g.^[18]

Figure 4 shows the metabolism of diethylene glycol and its possible effects.

MAIDEN PHARMACEUTICAL AND ITS CONTROVERSY!

Maiden Pharmaceutical has a controversial track record. The WHO report indicated that Maiden Pharma's plant was never certified by the UN agency. Maiden Pharma was one of the 46 Indian companies blacklisted by Vietnam in 2013. The contaminants of the drug by Maiden Pharma were so toxic according to the WHO that it resulted in 85% mortality, *The wire* reported. Most of the children who died of cough syrup made by Maiden Pharma and this cough syrup in Gambia were under 2 years of age. This seems to be the biggest stain on India's drug regulating agencies. For example, the company started operations in 1990 according to its website. The drug of maiden Pharma has been declared substandard since 2015 by



Hypocalcaemia, acute renal failure (ARF), neurological dysfunction, myocardial dysfunction, pulmonary dysfunction

Figure 3: Metabolism of ethylene glycol and its possible effects.

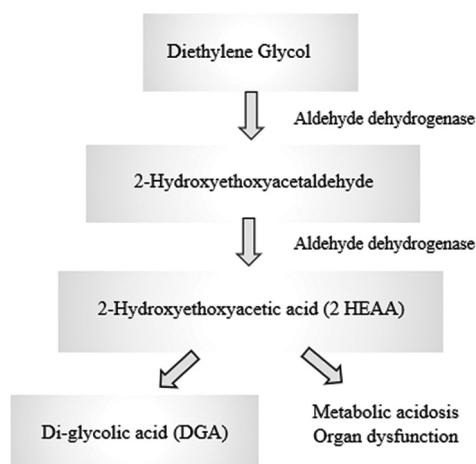


Figure 4: Metabolism of diethylene glycol and its possible effects.

the drug regulators of Kerala and Gujarat. Some of these substandard drugs were diabetes medication – metformin, Vitamin D and calcium tablets, and the blood thinner aspirin.^[19]

Maiden Pharma failed to produce logbooks

South first report the authorities, during the inspection, also found that the complete plant was under renovation. “The firm failed to produce the log books of equipment and instruments regarding manufacturing and testing for the drugs in question,” said the notice. It was also found that the batch numbers of the propylene glycol and sorbitol solution used in the manufacturing of cough syrups as excipients was not the same as the one mentioned on the Certificate of Analysis (CoA) report of the syrup. “Batch numbers of Propylene Glycol IP and Sorbitol Solution (70 %) IP in the CoA report number MPLR22031105 and MPLR22022301, respectively, was not found mentioned, which was used in the manufacturing of the drug in question.” Similarly, it was the case with batch numbers of Sodium Methyl Paraben IP in the CoA report.^[20]

What did the WHO say about Maiden Pharmaceutical Company?

The WHO issued a warning saying that four “contaminated” and “substandard” cough syrups produced by Maiden Pharmaceuticals Ltd, manufactured in the Indian state of Haryana, could be the cause of deaths in the West African nation of Gambia.^[21]

What did Central Drugs Standard Control Organization (CDSCO) say to WHO about Maiden Pharmaceutical Company?

Soon after the WHO issued a warning on four cough syrups made by Maiden Pharmaceuticals, India’s Drug Regulatory Authority, The CDSCO said that these drugs were exported only to The Gambia. The Health Ministry has ordered an inquiry into the incident. It said samples of four drugs have been sent to the Regional Drug Testing Lab, Chandigarh for testing. The results of that test were received by the WHO stating “four of the 23 samples under reference were found to have higher than normal amounts of either DEG or EG.” The exact one-to-one causal relationship of death has not yet been provided by the WHO.^[22]

Gambia said that there is “no confirmation” yet that 70 kids lost their lives due to cough syrup made in India

On November 2, 2022, the Medicine Control Agency of Gambia said that there was no confirmation that cough syrup made by Maiden Pharmaceuticals was the cause of death in children who died of AKI.^[23]

INDIA DRUG WATCHDOG UNDER SECURITY ONCE AGAIN

Another Indian biopharmaceutical company, Biocon was accused of bribing officials of the CDSCO. This is a flashback to May 2012, when the Parliamentary Standing Committee (PCC) on Health and Family Welfare presented a detailed report on the compromised drug regulatory system in India, exposing corruption between several pharma companies and CDSCO.^[24]

CHILD DEATHS IN GAMBIA: WHO BACKS CLAIMS OF “DANGEROUS” INDIAN COUGH SYRUP

The WHO tested a sample of the syrups (Promethazine Oral Solution, Kofexmalin Baby Cough Syrup, Makoff Baby Cough Syrup and Magrip N Cold Syrup) and found “unacceptable levels of DEG and EG as impurities”. DEG and EG are toxic to humans and can be fatal if ingested. India later said it was studying the product and ordered Maiden Pharmaceuticals to halt production at its main plant in northern Haryana. On December 13, India’s drugs controller general wrote to his WHO saying the samples tested in government laboratories were “uncontaminated”. “Test reports received by government laboratories found that all control samples of the four products met specifications,” he added.^[25]

WHO AGAIN ACCUSED ANOTHER INDIAN PHARMA COMPANY OF HAVING SUBSTANDARD MEDICINE

The WHO issued an Alert on January 11, 2023, that on December 22, 2022, two Substandard Medicines of Indian origin were found in Uzbekistan. Two products of Marion Biotech PVT Ltd (Uttar Pradesh, India) Ambronol Syrup and DOK-1 Max Syrup were found to be substandard. Till date, the said manufacturer has not given guarantees to the WHO on the safety and quality of these products.^[26]

REGULATORY AMENDMENTS FOR DEG AND EG IMPURITIES IN PHARMACEUTICAL PRODUCTS

In December 1997, International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) developed guidelines on impurities in drug substances and drug products to keep a check on the quality and contamination of pharmaceuticals. These guidelines, known as Q3A-Q3E, provide recommendations for the identification, qualification, and control of impurities in drug substances and drug products.^[27] Amendments

Table 2: Regulatory amendments for diethylene glycol and EG impurities in pharmaceutical products

Date	Reference number	Summary of amendment
October 15, 2018	25	Correction for the PDE and concentration limit for EG based on calculations in <i>Pharmeuropa</i> , Vol. 9, No. 1, Supplement, April 1997 S36
July 22, 2019	25	Reversion back to Q3C (R6) after archival searches related to the PDE for EG
October 4, 2019	25	Most recent amendment to the Q3C guideline related to EG
2010	26	IP monograph for EG sets a limit of 0.1% for DEG as an impurity
2010	26	IP monograph for DEG sets a limit of 0.1% for EG as an impurity
2010	27	USP updated guidelines for propylene glycol to specify limits for EG and DEG

EG: Ethylene glycol, DEG: Diethylene glycol, PDE: Permissible daily exposure, USP: United States Pharmacopoeia

in the Q3C guideline related to EG. The first reference which was made on 15 October 2018, Q3C(R7), had a correction for the permissible daily exposure (PDE) and concentration limit for EG based on calculations in *Pharmeuropa*, Vol. 9, No. 1, Supplement, April 1997 S36. The second reference, Q3C(R6), was reverted back to after archival searches related to the PDE for EG; and was provided in a cover statement dated July 22 2019. The most recent amendment to the Q3C guideline related to EG was on October 4, 2019. As per these guidelines and its amendments, the Permissible Daily Exposure (PDE) for EG is 6.2 mg/day, and the concentration limit for EG is 620 parts per million (ppm).^[28]

The IP monograph for EG in the sixth edition of the IP published in 2010 sets a limit of 0.1% for DEG as an impurity. The monograph also provides guidance on the use of gas chromatography and infrared spectroscopy for the detection and quantification of DEG.

Similarly, the IP monograph for DEG in the sixth edition of the IP published in 2010 sets a limit of 0.1% for EG as an impurity. The monograph also provides guidance on the use of gas chromatography and headspace gas chromatography for the detection and quantification of EG.^[29]

Propylene glycol, EG, and DEG can contain impurities that are harmful to human health. To address these concerns, the United States Pharmacopoeia (USP) updated its guidelines for propylene glycol in 2010, following recommendations from the US Food and Drug Administration (USFDA). The USP guidelines now specify limits for EG and DEG, which helps ensure that pharmaceutical products containing propylene glycol as an inactive ingredient meet quality standards and are safe for human use [Table 2].^[30]

In response to the tragic Gambia syrup incident that resulted in the death of over 100 children due to contaminated medication, the CDSCO implemented several amendments to improve drug safety and prevent similar incidents from occurring in the future. Recent amendments in regulations concerning excipients such as DEG and ethylene glycol (EG) aim to ensure the safety of pharmaceutical products by setting limits for these impurities, providing guidance

on their detection and quantification, and encouraging the use of advanced analytical techniques to assess their safety.

CDSCO has mandated stricter quality control measures for drug manufacturers, including regular inspections and testing of raw materials and finished products. This amendment also required manufacturers to maintain detailed records of their manufacturing processes and quality control procedures.

CDSCO established a new system for reporting adverse events related to drug use, which requires health-care providers to report any suspected adverse reactions to drugs within a specified timeframe. This amendment also introduced penalties for manufacturers who fail to report adverse events or who provide false information about the safety of their products. CDSCO increased its post-market surveillance activities to monitor the safety and effectiveness of drugs on the market has also been increased. Despite of all these actions, there is still more work to be done to ensure that all drugs on the market are safe and effective for use by the public.

CONCLUSION

DEG and ethylene glycol (EG) are widely used excipients in pharmaceuticals, cosmetics, and other industrial applications due to their favorable physical and chemical properties. However, their toxicity and potential for contamination pose significant challenges in their utilization. There are many such solvents which are used for manufacturing drugs that may prove to be lethal in case of no quality check by the quality control personnel. DEG has been responsible for large-scale poisoning outbreaks that have claimed many lives in one way or another. Given the history of DEG, it is usually associated with contaminated medicines. Because of these epidemics, about 1 mL/kg of body weight (perhaps much less) is thought to be a lethal dose for some people. Therefore, it is crucial to establish appropriate quality control measures, including rigorous testing and monitoring, to ensure their safe use. In addition, alternative excipients should be explored and developed to mitigate the risks associated with DEG and EG usage. Overall, a thorough understanding of the challenges and limitations of using

DEG and EG as excipients is necessary to make informed decisions and ensure product safety and efficacy.

CONFLICT OF INTEREST STATEMENT

The authors have declared that no competing interests exist.

REFERENCES

- Gambia Says Child Deaths Linked to Cough Syrup have Risen to 70. *The Economics Times*; 2022. Available from: <https://health.economictimes.indiatimes.com/news/pharma/gambia-says-child-deaths-linked-to-cough-syrup-have-risen-to-70/94870688> [Last accessed on 2023 Jan 13].
- World Health Organization. Medical Product Alert N°6/2022: Sustandard (Contaminated) Paediatric Medicines. Geneva: World Health Organization; 2022.
- Araujo SA, Vasconcelos JC, Wanderley DC, Silva AC. Renal Toxicity Caused by Diethylene Glycol: An Overview. North Carolina: Research Square; 2022.
- Rentz ED, Lewis L, Mujica OJ, Barr DB, Schier JG, Weerasekera G, *et al.* Outbreak of acute renal failure in Panama in 2006: A case-control study. *Bull World Health Organ* 2008;86:749-56.
- Alfred S, Coleman P, Harris D, Wigmore T, Stachowski E, Gaudins A. Delayed neurologic sequelae resulting from epidemic diethylene glycol poisoning. *Clin Toxicol* 2005;43:155-9.
- Alkahtani S, Sammons H, Choonara I. Epidemics of acute renal failure in children (diethylene glycol toxicity). *Arch Dis Child* 2010;95:1062-4.
- Kraut JA, Kurtz I. Toxic alcohol ingestions: Clinical features, diagnosis, and management. *Clin J Am Soc Nephrol* 2008;3:208-25.
- Global Diethylene Glycol Market Outlook Extensive Use in Personal Care and Cosmetics Products. Available from: <https://www.expertmarketresearch.com/reports/diethylene-glycol-market> [Last accessed on 2022 Dec 03].
- Diethylene Glycol Market Information by Application (Plasticizer, Personal Care, Chemical Intermediates, & Polyester Resins), End-Use Industries (Building and Construction, Plastics, Paints and Coatings, & Polymers), and Region—Forecast till. Market Research Future. Available from: <https://www.marketresearchfuture.com/amp/reports/diethylene-glycol-deg-market-1713> [Last accessed on 2022 Dec 14].
- MDPI. A Review of Recent Developments of Pervaporation Membranes for Ethylene Glycol Purification. Available from: <https://www.mdpi.com/2077-0375/12/3/312> [Last accessed on 2022 Dec 25].
- Schep LJ, Slaughter RJ, Temple WA, Beasley DM. Diethylene glycol poisoning. *Clin Toxicol* 2009;47:525-35.
- Bowie MD, Mckenzie D. Diethylene glycol poisoning in children. *S Afr Med J* 1972;46:931-4.
- Cantarell MC, Fort J, Camps J, Sans M, Piera MR. Acute intoxication due to topical application of diethylene glycol. *Ann Intern Med* 1987;106:478-9.
- Okuonghae HO, Ighogboja IS, Lawson JO, Nwana EJ. Diethylene glycol poisoning in Nigerian children. *Ann Trop Paediatr* 1992;12:235-8.
- Hanif M, Mobarak MR, Ronan A, Rahman D, Donovan JJ, Bennis ML. Fatal renal failure caused by diethylene glycol in paracetamol elixir: The Bangladesh epidemic. *BMJ* 1995;311:88-91.
- Diethylene_glycol @ en.wikipedia.org. Wikipedia; 2022. Available from: https://en.wikipedia.org/wiki/Diethylene_glycol#cite_note-0-71 [Last accessed on 2023 Jan 11].
- Jamison CN, Dayton RD, Latimer B, McKinney MP, Mitchell HG, McMartin KE. Diethylene glycol produces nephrotoxic and neurotoxic effects in female rats. *Clin Toxicol* 2022;60:324-31.
- Jamison CN, Dayton RD, Latimer B, Mckinney MP, Mitchell HG, Mcmartin KE, *et al.* Neurotoxic effects of nephrotoxic compound diethylene glycol neurotoxic effects of nephrotoxic compound diethylene glycol. *Clin Toxicol (Phila)* 2021;59:810-21.
- Sharma A. The Controversial Track Record of Maiden Pharma. CNBCTV18; 2022. Available from: <https://www.cnbctv18.com/healthcare/the-controversial-track-record-of-maiden-pharma-14907201.htm> [Last accessed on 2023 Jan 20].
- Belagere C. Maiden Pharma: Why Should Your License not be Suspended/Cancelled, Asks CDSCO Show Cause Notice. South First; 2022. Available from: <https://thesouthfirst.com/health/maiden-pharma-case-explain-why-your-manufacturing-license-may-not-be-suspended-cancelled-asks-cdscos-show-cause-notice-to-drug-company> [Last accessed on 2023 Jan 28].
- WHO Alert on Cough Syrups “Alarming”; There are Missing Links that Need to be Probed: Expert; 2022. Available from: <https://www.thehindu.com/news/national/who-alert-on-cough-syrups-alarming-there-are-missing-links-that-need-to-be-probed-expert/article65984447.ece> [Last accessed on 2023 Feb 02].
- WHO Alert: Regulatory Body Says Syrups Sent Only to Gambia. *The Economics Times*; 2022. Available from: <https://economictimes.indiatimes.com/industry/healthcare/biotech/pharmaceuticals/who-alert-regulatory-body-says-syrups-sent-only-to-gambia/articleshow/94690547.cms?from=mdr> [Last accessed on 2023 Feb 04].
- Gambia Says ‘No Confirmation’ India-made Cough Syrup Killed 70 Kids. *Mint*; 2022. Available from: <https://www.livemint.com/news/world/gambia-says-no-confirmation-india-s-maiden-pharmaceuticals-made-cough-syrup-killed-70-kids-11667401163470.html> [Last accessed on 2023 Feb 15].
- Roychowdhury V. India’s Medicine Watchdog Under the Scanner Once Again. *Express Pharma*; 2022. Available from: <https://www.expresspharma.in/indias-medicine-watchdog-under-the-scanner-once-again> [Last accessed on 2023 Feb 22].
- Gambia Child Deaths: WHO Stands by “Dangerous” India Cough Syrup Claim. *BBC News*; 2022. Available from: <https://www.bbc.com/news/world-asia-india-63996180> [Last accessed on 2023 Feb 25].

26. Medical Product Alert N°1/2023: Substandard (Contaminated) Liquid Dosage Medicines; 2023. Available from: [https://www.who.int/news/item/11-01-2023-medical-product-alert-n-1-2023-substandard-\(contaminated\)-liquid-dosage-medicines](https://www.who.int/news/item/11-01-2023-medical-product-alert-n-1-2023-substandard-(contaminated)-liquid-dosage-medicines) [Last accessed on 2023 Mar 04].
27. Services H. Guidance for Industry Q3C Impurities: Residual Solvents. United States: U.S. Department of Health and Human Services; 1997.
28. ICH Expert Working Group. ICH Harmonised Guideline-Impurities: Guideline for Residual Solvents Q3C(R8). United States: International Council on Harmonisation Technical Requirements for Pharmaceuticals for Human Use; 2021. p. 1-43.
29. The Indian. Indian Pharmacopoeia; 2010. p. 753. [Last accessed on 2023 Apr 12].
30. PerkinElmer. The Limit of Ethylene Glycol and Diethylene Glycol. AZO Materials. Available from: <https://www.azom.com/article.aspx?articleid=21957> [Last accessed on 2023 Feb 12].