



REVIEW ARTICLE

Diethylene Glycol Poisoning – Past to Present

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Probably we all have heard many depressing stories already about deadly cough syrup adulterated with Diethylene Glycol (DEG). DEG is a very infamous and dangerous chemical used for mostly preparing pharmaceutical products and consumer products. DEG makes it an excellent counterfeit for pharmaceutical-grade glycerine or propylene glycol, it has a sweetish taste which makes DEG suitable for pharmaceutical preparations. It had been in news for a long back from The Massengill Incident to the recent Gambia tragic incident. The hallmark of DEG poisoning is Acute Renal Failure (ARF). Over the years, DEG has been loaded into all varieties of medicine such as cough syrup, fever medication, injectable drugs, etc. although the batch of the adulterated medicines was recalled after the alert by the time it was recalled it has already caused damage hence, it's not allowed to use in food and drugs by many Health authorities. WHO had warned on time to Health Authorities regarding DEG Mass poisoning. Despite so many tragic incidents and deaths in multiple countries, there is still a lack of regulation for using DEG for pharmaceutical preparations. The generation of scientific knowledge and strict regulation required worldwide to control mass poisoning so that medicines can benefit humankind greatly instead of harming them.

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Introduction

Diethylene glycol (DEG) is an organic compound. The Chemical formula of DEG is (HOCH₂CH₂)₂O also known as DEG, 2, 2-oxy-di-ethanol, and DEGlycol. By nature, it's practically odorless, colorless, hygroscopic liquid with a sweetish taste and poisonous. It is miscible in water, alcohol, ether, acetone, and ethylene glycol which makes it a useful industrial chemical. DEG is also widely used as a solvent spanning back to 1937. (Marraffa. J. 2014)

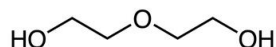


Figure 1: Diethylene Glycol

it is a by-product of the production process of mono ethylene glycol (MEG). The process consists of the oxidation of ethylene at a high temperature in the presence of a silver oxide catalyst. The ethylene oxide is then hydrated to yield diethylene glycol with mono-ethylene glycol and tri-ethylene glycol as co-products. (The Chemical Company, 2022)

Toxicology of DEG

The information available regarding human toxicity is very limited Despite the Elixer Sulfanilamide tragedy, 1937 Mass poisoning around the world. The study suggests the maximum toxic dose is estimated at 0.14 mg/Kg of body weight and the toxic dose is between 1.0 and 1.62 g/kg of body weight. (Kraut et al, 2007)



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Whereas some study suggests the toxic dose in adults is ~1mL/kg. (Marraffa J.M., 2008) and others suggest this is a toxic dose. It has many serious Adverse Effects hence it is not allowed to use in food and drugs by many drug regulatory bodies e.g. The Therapeutic Goods Administration (TGA) Australia does not allow DEG as a food additive due to its toxicity. The USFDA allows no more than 0.2 % of DEG. (CFR - Code of Federal Regulations, 2022)

Mechanisms of toxicity

The Mechanism of toxicity of DEG is not very clear but the latest research suggests that the DEG metabolite, HEAA, is the major contributor to renal and neurological toxicities. (Schep et al., 2009)

The clinical effects of DEG poisoning can be divided into three stages:

First phase

The first phase shows the gastrointestinal symptoms e.g., nausea, vomiting, abdominal pain, and diarrhea develop. Some patients can also develop neurological symptoms e.g., inebriation, altered mental state, etc.

Second Phase

The second phase consists of metabolic acidosis and if the poisoning is known patient can develop more severe metabolic acidosis and renal injury and in the absence of supportive care, can also lead to death.

Third Phase

If patients are stabilized, they may then enter the final phase with various delayed neuropathies and other neurological effects, which are sometimes fatal. The mean estimated fatal dose in an adult has been defined as approximately 1 mL/kg of pure DEG. (Schep et al., 2009)

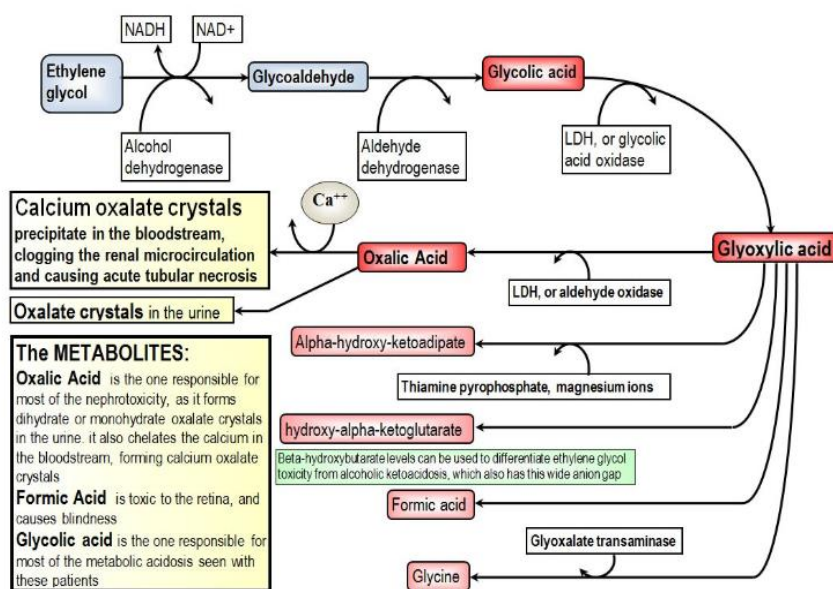


Figure 2: Mechanism of toxicity

Management

The Initial management of DEG poisoning consists of providing initial support case with the proper airway management, attention to correcting acid-base status serum electrolytes, and fluid balance. The necessary treatment may include the prompt use of fomepizole or ethanol which is important in preventing the formation of the toxic metabolite HEAA; hemodialysis can also be critical and assisted ventilation may also be required. (Minns A, 2012)

Epidemiology of DEG poisoning in past

The physical-chemical properties of DEG make it an excellent counterfeit for pharmaceutical-grade glycerine (also called glycerol) or propylene glycol and have caused many deaths in different countries. Incidents include its use of DEG in China as a component of cheap toothpaste, and by winemakers in Europe as an adulterant to create a "sweet" wine.

The Massengill Incident (United States):1937

In June 1937, a salesman for the S.E. Massengill Co., in Bristol, Tenn., reported a demand in the southern states for a drug called Sulfanilamide, (a drug used to treat streptococcal infections), in liquid form.



Figure 3: Newspaper coverage of The Massengill Incident

The company experimented and found that sulfanilamide would dissolve in diethylene glycol. the new liquid formulation was not tested for safety and toxicity. The elixir shipments were sent all over the country. On October 11, the American Medical Association (AMA) received reports from physicians in Tulsa, Okla., that an unfamiliar sulfanilamide compound was responsible for several deaths. The AMA asked for samples of the drug and then wired the Massengill Co., requesting the composition of the compound. (Ballentine C., 1981) The AMA laboratory isolated diethylene glycol as the toxic ingredient and immediately issued a warning, through newspapers and radio, that Elixir Sulfanilamide was toxic and deadly.

South Africa:1969

In 1969, 7 children presented with vomiting, deterioration in the level of consciousness, and oliguria diminishing to anuria. On admission, they were found to be dehydrated with a profound metabolic acidosis, a raised blood urea, and a transaminase level. Hepatomegaly was present in all, and in some enlarged kidneys could be palpated. The clinical course was inexorable, and death followed in a few days, despite treatment and the correction of metabolic abnormalities. (Bowie et al., 1972)

Spain: 1985

The Patients who were being treated for the burns suddenly developed anuric kidney failure. In further investigation, it was noticed that all the patients who were treated with the ointment (Sulfadiazine) contained DEG (Di ethylene Glycol). There were 5 Deaths involved in this incident. (Okuonghae et al., 1992)

Wine scandal (Austria and Germany):1985

In July 1985, the DEG was allegedly used as a sweetening agent has been found in wine in Austria and Germany. In November, The New York Times published a wine recall that the Federal Government released after the Bureau of Alcohol, Tobacco, and Firearms. (Casco et al., 2015)

India:1986

1986 in Mumbai where 14 patients died of renal failure at the state-run JJ Hospital. The suspected glycerine with which the patients were being treated was contaminated with diethylene glycol consumption which can be fatal for human beings. The glycerine was administered orally to treat glaucoma and coughs and used as a laxative. The post-mortem reports showed that all 14 had died of cortical necrosis. (Barnagarwala T., 2022)



Figure 4: Media Coverage of JJ Hospital tragedy

Nigeria: 1990

From June to September 1990, 47 children died in a hospital in Nigeria allegedly from paracetamol syrup which was adulterated with Diethylene glycol. Many children presented with fever, vomiting, diarrhea, and convulsions. The Laboratory findings included hyperkalemia, acidosis, elevated creatinine level, and hypoglycemia. Management consisted of correction of dehydration and acidosis plus administration of antibiotics when indicated. None of the children had dialysis. All children died within 2 weeks of hospital admission. (Okuonghae et al., 1992)

Bangladesh: 1990–1992

In Bangladesh between 1990 and 1992, after being given paracetamol (acetaminophen) syrup contaminated with diethylene glycol. (Hanif et al., 1995) 339 children developed kidney failure, and most of them died, the outbreak forced the government to ban the sale of paracetamol elixirs in December 1992, eventually, there was a decline of 53 percent in the hospital admission of patients with renal failure and 84 percent decline in hospital admissions by unexplained renal failure. (Hanif et al., 1995)

Argentina: 1992

15 Patients died due to Propolis syrup contamination with DEG in Argentina. Propolis is a resin elaborated by bees, used to build their beehives, with antimicrobial, anti-inflammatory, and antioxidant properties. During the analysis of the samples found that the syrup contained 55% DEG (w/v). ([SCCP opinion on Deg, 2008](#))

Haiti: 1995–1996

From November 1995 through June 1996, acute anuric renal failure was diagnosed in 86 children (aged 3 months–13 years) in Haiti. The Ministry of Health of Haiti initiated an investigation. The report summarizes that this outbreak was associated with diethylene glycol (DEG)-contaminated glycerin used to manufacture acetaminophen syrup. The investigation also revealed that at least 79% of patients had consumed one of two locally manufactured acetaminophen syrup preparations ("Afebril" and "Valodon"). The manufacturing company announced a recall of these and other syrup products it produces. With the recall and an ongoing public information campaign, the number of new cases declined sharply. ([CDC, 1996](#))



Figure 5: Afebril and Valodon contaminated with DEG

China: 2006

Wang Guiping, an ingredient supplier falsified his license and lab reports. Wang made syrup for the company Qiqihar Pharmaceutical which was in the top 2 in 2005. Wang found a reference to diethylene glycol in a chemical book. After manufacturing the second batch of syrup containing diethylene glycol for Qiqihar Pharmaceutical, no test was performed. The counterfeit syrup ended in ampules of Amillarisin A, a medication for gall bladder problems; especially pediatric enema fluid; blood vessel disease injections; intravenous pain reliever; and an arthritis medication. In April 2006, the Guangdong Province Hospital of Guangzhou began administering Amillarisin A to their patients. Soon thereafter, many patients died after receiving the medication. Mr. Wang was caught, and Qiqihar was shut down by the authorities. It was said by the researchers that, the kidneys fail first. Then the central nervous system begins to misfire.

Paralysis spreads, making breathing difficult, which is often impossible without assistance. In the end, most victims die. The researchers said thousands of patients died in this tragedy. ([Bogdanich et al., 2007](#))

Panama: 2006

In Panama in 2006, 43 people died after consuming adulterated medicine. The in-depth investigation by health authorities revealed that the cause of death was found to be an ordinary, government-produced, cough syrup. However, the deadly cough syrup differed from legitimate medicine by one key ingredient. Harmless and commonly used Glycerine was substituted for a cheaper, poisonous alternative: Diethylene Glycol. ([ICC, 20017](#))

Worldwide toothpaste incident: 2007

In May 2007, toothpaste was labeled as it's containing DEG. On June 1, 2007, the USFDA warned consumers to avoid toothpaste which is from China. There was not much information on the status of these kinds of toothpaste shipments in the US but as a precautionary measure authorities started testing all the imported Chinese toothpaste. A few days later, Colgate-Palmolive found counterfeit toothpaste with its name, which was contaminated with DEG and was found at dollar-type discount stores in New York, New Jersey, Pennsylvania, and Maryland. But the case with the event. Although there were no reports that anyone was harmed, several people in the eastern US reported experiencing Pain and Headache after using the product. It was later discovered that a great number of tubes with poison ended up in hospitals for the mentally ill, prisons, juvenile detention centers, other hospitals, and many other state institutions. The public outcry worldwide made Chinese officials ban the practice of using diethylene glycol in toothpaste. ([Worldwide toothpaste incident, 2007](#))

Nigeria: 2008

On November 18, 2008, the Nigerian Health authority (FMOH) received a report of 13 cases of unexplained acute renal failure among children from a hospital in Lagos state. Few patients had a medication history of a liquid acetaminophen-based teething medication. The Nigerian health authority inspected and found diethylene glycol (DEG) in four batches of teething medication. An investigation was launched by the Nigeria Health Authority. This report summarizes the results of the investigation, which shows 57 cases of DEG poisoning among children aged ≤ 3 years from August 2008--January 2009, of whom 54 died. Of the 57 children with DEG poisoning, 96 % had exposure to acetaminophen-based teething medication (My Pikin). DEG contamination was identified in six bottles of the medication from patient households and four batches from the facility in which the medication was manufactured. ([CDC, 2009](#))

Brazil: 2019/2020

December 30, 2019. Few patients had reported symptoms such as nausea, vomiting, abdominal pain, acute kidney failure, facial nerve paralysis, blurred vision, temporary blindness, and sensory changes in a city in Brazil. The Police investigating found traces of DEG in Brazilian craft brewer Backer found traces of diethylene glycol (DEG) in a Brazilian brand beer. The Ministry of Agriculture, Brazil said all products from the brewery had been recalled and production suspended. The investigation report revealed that DEG had been used as a coolant for the brewery equipment, in what should have been a closed circuit, but an undetected leak in the system contaminated some batches of beer. Six patients died by consuming contaminated beer. (Sanchez et al., 2020)

India: 2020

In January 2020 around 17 children from Ramnagar in Jammu and Kashmir were hospitalized with symptoms of acute kidney failure. It was reported that almost 10 children in the age group of six months to six years died within 15 days. An investigation team was sent a team to Ramnagar. And the investigation report revealed the presence of Diethylene Glycol (DEG), in the Coldbest-PC syrup administered to cure colds and fever among these children. Early in February 2020 a joint inspection with a team from CDSCO was carried out at the manufacturing facility. The manufacturer failed to provide some documents. The manufacturing was stopped, and records were seized as per the report. (Raghavan P., 2022)

India/Gambia/Indonesia: 2022

This is a recent tragic incident. A cough syrup killed 69 children in Gambia. The story goes that these syrups contained unacceptable amounts of preservatives, most notably diethylene glycol and ethylene glycol. The syrup is manufactured by an Indian company- Maiden Pharmaceuticals. Name Kofexmalin Baby Cough Syrup, Makoff Baby Cough Syrup, and Magrip N Cold Syrup. The pictures of the product has been presented in Figure 6. As per a report by the Manufacturer, Maiden Pharmaceuticals was blacklisted for supplying substandard drugs to the Bihar government back in 2011. Unfortunately, how did Maiden Pharmaceuticals continue to operate despite being red flagged on multiple occasions, No one knows? (Thiagarajan et al., 2022)



Figure 6: Kofexmalin baby cough syrup, Makoff baby cough syrup, Magrip N cold syrup contaminated with DEG

Subsequently, on 21 October 2022, 99 children were reported dead in Indonesia after ingesting the cough syrups. The health authority of Indonesia banned all cough syrup in the country. (Mao B. F., 2022)

Conclusion

It seems that DEG (diethylene glycol) is a serial offender from the back 1937 to 2022. DEG ingestion had led to serious fatal complications in past. Every time it's innocent patients, most of them are children who are the victim. Although the products were recalled it will never eliminate the risk. The Use of safe manufacturing practices by the manufacturer might have prevented such a tragic event. We are in extreme need of strict guidelines, more uniform regulations, and international cooperation for the prevention of these incidents. Most of the time it's adulterated drug preparations that prove, there are loopholes in our quality control and quality assurance system. The regulations must inspect manufacturers promptly to prevent such tragic incidents in near future. Countries which are inadequately implemented safe manufacturing standards, poorly enforce quality controls, or lack adequate training programs will remain at risk for medication-associated poisonings.

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Conflict of interest

Nil

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