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Ban Cough Syrup 2022 Review

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Abstract

The contamination of cough syrups manufactured in Haryana was recently reported. The four cough and cold syrups so contaminated as to be banned by the WHO are Promethazine Oral Solution, Kofexmalin Baby Cough Syrup, Makoff Baby Cough Syrup, and Magrip N Cold Syrup. India-made cough and cold syrups are "potentially linked with acute kidney injuries and 70 children`s deaths" and will be distributed in The Gambia in 2022. According to the WHO, diethylene glycol and ethylene glycol are toxic to humans when consumed and can be fatal. This incident includes the prevalent proportion of cases with neurotoxic signs and symptoms

Keywords: Cough Syrup; Diethylene glycol; Ethylene glycol; Promethazine

1. Introduction

A drug is "a chemical or synthetic substance used to restore health, avoid or analyse disease, or otherwise contribute to physical or mental well-being. Banned medicines are those that are not permitted to be consumed because they may unnaturally boost performance and exhibit a variety of detrimental consequences in addition to therapeutic ones. The World Health Organisation (WHO) issued a global notice after four of Maiden's cough syrups were related to over 70 children's fatalities. In India, investigations are now underway. In addition to acute renal impairment, a significant number of individuals with diethylene glycol intoxication experienced progressive neurologic signs and symptoms [1].

Figure 1 Cough Syrup

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1.1. Diethylene glycol

Diethylene glycol is a transparent liquid that is frequently used as a diluent in industry. In humans, it has significant nephrotoxic and neurotoxic effects [1]. Diethylene glycol consumption can cause acute tubular necrosis, which can lead to kidney damage, as well as neurologic symptoms such as acute flaccid paralysis, cranial nerve palsies, and encephalopathy. Intentional intake of industrial items containing diethylene glycol has very rarely resulted in diethylene glycol poisoning. Contrarily, the majority of cases of diethylene glycol poisoning are brought on by pharmaceutical products that use diethylene glycol as a diluent rather than a secure substance like pharmaceutical-grade glycerine or propylene glycol. Mass poisoning occurrences are a normal outcome of sharing and human usage (2–18). Diethylene glycol outbreaks that have recently occurred [2].

1.1.1. Preparation

DEG is produced via the fractional hydrolysis of ethylene oxide. Variable levels of DEG and related glycols are generated depending on the circumstances. The resulting manufactured good consists of two ethylene glycol molecules linked by an ether bond. Diethylene glycol is produced as a byproduct of ethylene glycol and triethylene glycol (MEG). The manufacturing process is usually designed to optimise MEG production. Ethylene glycol accounts for the vast majority of glycol products used in a range of applications. DEG accessibility will be determined by the demand for derivatives of the principal commodity, ethylene glycol, rather than by DEG market requirements.

1.1.2. Uses

Diethylene glycol is a chemical that is used to make saturated and unsaturated polyester resins, polyurethanes, and plasticizers. DEG is a building block in organic synthesis, such as the production of morpholine and 1,4-dioxane. It can be used to dissolve nitrocellulose, resins, pigments, oils, and other organic substances. Tobacco, cork, printing ink, and glue use it as a humectant. It's also in brake fluid, lubricants, wallpaper removers, fog and haze treatments, and heating and cooking fuel. DEG is frequently replaced with chosen diethylene glycol ethers in personal care products (e.g., skin creams and lotions, deodorants). Although a dilute solution of diethylene glycol can be employed as a cryoprotectant, ethylene glycol is far more routinely used. Most ethylene glycol antifreezes contain a trace of diethylene glycol.

1.1.3. Toxicology

Despite the discovery of DEG's toxicity in 1937 and its relation to mass poisonings all over the world, the information available on human toxicity is sparse. According to some publications, the least hazardous dose is 0.14 mg/kg of body weight and the lethal dose is between 1.0 and 1.63 g/kg of body weight, while others claim the LD50 in humans is 1 mL/kg, while others claim this is the LD30. Because of its negative effects on people, diethylene glycol is not permitted for use in food or drugs [3] (in many countries). When used as a food additive, the US Code of Federal Regulations allows no more than 0.2% diethylene glycol in polyethylene glycol. [4]

In animal studies, diethylene glycol had "moderate to low" acute toxicity. The LD50 for small mammals has been determined to be between 2 and 25 g/kg, making it less hazardous than its relative, ethylene glycol, but still capable of causing poisoning in humans (in high concentrations only). [5] According to oral toxicity findings in laboratory animals, diethylene glycol appears to be more dangerous to humans [6].

1.1.4. Absorption and distribution

The principal method of absorption is oral ingestion. Except when applied to broken or injured skin, dermal absorption is exceedingly limited. DEG is absorbed by the gastrointestinal system and transported throughout the body by the circulation, reaching peak blood concentrations about 30 to 120 minutes after intake. Enzymes metabolise DEG after it reaches the liver.

1.1.5. Metabolism and elimination

Initially, scientists believed that DEG was converted into ethylene glycol, which is dangerous due to the metabolic synthesis of glycolic acid, glycooxylic acid, and finally oxalic acid. The accumulation of glycolic acid in the body is the primary cause of ethylene glycol toxicity; however, calcium oxalate crystals in the kidneys can also induce acute renal failure. In the case of DEG, investigations revealed no calcium oxalate crystal formations in the kidneys, showing that ethylene glycol is not part of the DEG metabolic pathway. According to rat models, DEG is metabolised in the liver by the enzyme NAD-dependent alcohol dehydrogenase (ADH) into a hydrogen ion, NADH, and 2-hydroxyethoxyacetaldehyde ($C_4H_8O_3$). Soon after, the enzyme aldehyde dehydrogenase metabolises 2-hydroxyethoxyacetaldehyde ($C_4H_8O_3$) (ALDH) [7, 8].

1.2. Ethylene glycol

When swallowed, ethylene glycol has a moderately high mammalian toxicity, comparable to methanol, with an oral LDLo of 786 mg/kg for humans [9]. The primary concern is that its sweet taste attracts youngsters and animals. Upon intake, ethylene glycol is oxidised to glycolic acid, which is then converted to oxalic acid, which is poisonous. It and its poisonous byproducts initially damage the central nervous system, then the heart, and eventually the kidneys. If consumed in significant quantities, it is lethal if left untreated [10]. Each year, many deaths are reported in the United States alone [11, 12].

There are antifreeze formulations for automobile usage that include propylene glycol instead of ethylene glycol. They are typically regarded as safer to use because propylene glycol is less palatableand is transformed.

1.2.1. Use

Coolant and heat-transfer agent

The primary application of ethylene glycol is as an antifreeze agent in coolants used in automobiles and air-conditioning systems that either place the chiller or air handler outside or must cool below the freezing temperature of water. Ethylene glycol is the fluid that carries heat in geothermal heating and cooling systems via a geothermal heat pump. Depending on whether the system is used for heating or cooling, the ethylene glycol either acquires energy from the source (lake, ocean, or water well) or dissipates heat to the sink.

The specific heat capacity of pure ethylene glycol is around half that of water. As a result, ethylene glycol reduces the specific heat capacity of water mixes while offering freeze protection and a higher boiling point [13, 14].

1.2.2. Environmental effects

Ethylene glycol is a high-volume chemical that degrades in about 10 days in the air and a few weeks in water or soil. It enters the environment through the dissemination of ethylene glycol-containing goods, particularly at airports where it is employed in runway and aeroplane de-icing chemicals [14]. While ethylene glycol is not hazardous at low dosages for long periods of time, it is a teratogen at high levels (1000 mg/kg per day). "It generates skeletal abnormalities and deformities in rats and mice across all routes of exposure, according to a very broad database". This molecule has been spotted in space [15, 16, 17, 18].

1.2.3. Signs and symptoms

The first stage is characterised by gastrointestinal symptoms such as nausea, vomiting, abdominal discomfort, and diarrhoea. Early neurological signs such as altered mental state, central nervous system depression, coma, and moderate hypotension may occur in certain people.

Second phase: One to three days after consumption (depending on the dose), patients develop metabolic acidosis, which causes acute renal failure, oliguria, rising serum creatinine levels, and subsequently anuria. Other signs of acidosis and/or renal failure include hypertension, tachycardia, cardiac dysrhythmia, pancreatitis, hyperkalemia, and moderate hyponatremia.

Final phase: At least five to ten days after consumption, the majority of symptoms are related to neurological problems, such as increasing lethargy, facial paralysis, dysphonia, dilated and nonreactive pupils, quadriplegia, and death [19, 20].

1.2.4. Etiology

Table 1 Summary data of ban cough syrup

Year	Country	Reported Number Possible DEG Poisoning Cases	Reported Number Possible DEG Poisoning Deaths	Reference
1937	USA	260	105	3,4
1996	South Africa	No Reported	7	21
1986	India	14	14	5
1987	Spain	05	05	6

1990	Nigeria	47	47	7
1990	Bangladesh	67-339	51-236	8
1992	Argentina	29	29	9
1995	Haiti	87-109	85	10,11
1998	India	36	33	12
1998	India	11	08	13
2006	Panama	119	78	14
2008	China	15	12	22,23
2008	Nigeria	60	57	17,18
2022	India (Hariyana)	80	40	24,25

2. Conclusion

In addition to acute renal impairment, a large proportion of individuals with diethylene glycol intoxication experienced progressive neurologic signs and symptoms. Clinicians should evaluate diethylene glycol poisoning if there is facial or limb paralysis combined with an unexplained acute renal injury. Elevated CSF fluid protein concentrations in diethylene glycol-exposed people with acute renal injury without pleocytosis may be a predictor of progressive neurologic disease.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

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