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Cough Syrup or Death Syrup: The Need of Forensic Pharmacovigilance

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Abstract

This article explores the global issue of contaminated and adulterated cough syrups with a particular focus on affected regions such as Asia, Africa, and America. It examines the prevalence and risks associated with different adulterated and contaminated cough syrups, uncovered to contain ethylene glycol and diethylene glycol, toxic substances used as industrial solvents and antifreeze agents, heavy metals, nitrosamine contaminants, active drugs and other contaminants that can be fatal even when taken in small amounts, especially for children under the age of twelve. This has sparked the interest of the World Health organisation in investigating the production and supply chains of medicines with standard quality measures, with assistance from the FDA and the Indian CDSCO health organization in strict regulatory enforcement to ensure drug safety. The article discusses the forensic approach for pharmacovigilance and analysis of such cough syrups in the purview of pharmaceutical toxicology. Moreover, the article discusses collaborative efforts of health organizations worldwide to heighten surveillance, improve inspection protocol and ensure that drugs be tested with utmost rigorousness. This article concludes by emphasizing the need for robust regulatory frameworks to protect public health and prevent future incidents. By addressing this pressing issue, the article aims to inform readers about the dangers of adulterated pharmaceuticals and the ongoing global efforts to mitigate them.

Keywords: Cough Syrup; Over the Counter; Forensic Pharmacovigilance; Glycols; Adulterant; Contaminant

Abbreviations

WHO: World Health Organization; EG: Ethylene Glycol; DEG: Diethylene Glycol; TRPV1: Transient Receptor Potential Vanilloid 1.

Introduction

Cough syrup is a liquid medication designed to relieve cough symptoms, and it can either suppress the cough or make a cough productive by thinning mucus [1]. Coughing is a largely uncontrolled, protective reflex mechanism responsible for mucociliary clearance of the airway and excess secretions within the airway [2]. Cough is one of the most common medical complaints and symptoms of respiratory tract infections for which patients seek relief. Although usually self-limited, coughing can keep the patient awake or cause absence from work or school due to fatigue [3]. A cough syrup is a must-have for new moms, old moms, and everyone in general, as everyone has their share of

suffering from a cough, either once or twice.

Cough syrups have been manufactured by pharmaceutical companies, across the globe by Johnson & Johnson and Pfizer, have maintained a strong reputation for their extensive and efficient production. A significant portion of this production is based in Asia—especially India—which has emerged as one of the world's largest producers of pharmaceuticals, including cough syrups. While production has generally proceeded smoothly, recent concerns have arisen regarding the safety of certain cough syrups. Alarming reports surfaced when cough syrup brands were found to contain diethylene glycol, a toxic substance.

This prompted both the Indian government and the World Health Organization (WHO) to issue warnings.

Disturbingly, this is not the first time such an incident has occurred. Similar toxic substances have previously been found in medicinal syrups produced in India—the world's largest exporter of generic drugs.

Pharmaceutical contamination may result from mislabeling, unintentional production mistakes, or manufacturers intentionally contaminating the product for economic gain. Compliance with predetermined quality standards is just one method of monitoring and detecting adulteration or contamination of items. Several international public health organizations, including the US Food and Drug Administration and the World Health Organization, have issued alerts, recommendations, and instructions for the concerned parties in order to fight against such contaminations. The Drugs and Cosmetics Act, 1940 very clearly outlines the division of responsibilities as far as drug control in India is concerned. Two key bodies, Central Drugs Standard Control Organization and State Drug Regulatory Authorities, are entrusted with this task. At the national level, CDSCO oversees setting standards for drugs, controlling the quality of imported drugs, and approving new drugs and clinical trials. SDRAs monitor the manufacturing, selling, and distribution of drugs. Indian Pharmacopoeia forms the official drug standards in this statutory framework that ensures the efficacy and safety of medicines in India.

A recent case of ColdRif, a cough syrup produced in India has been found to be adulterated with DEG beyond permissible limit, caused the kidney failure deaths of 23 children in total in the states of Kerala, Madhya Pradesh and Tamil Nadu, leaving several of others battling for their lives in hospitals [4]. In a notable case between June and September 2022, at least 66 children in The Gambia died after consuming contaminated syrups produced by Maiden Pharmaceuticals [5], where WHO's analysis confirmed the presence of unacceptable levels of DEG and EG, which are toxic and potentially fatal [6-9]. In an incident in Uzbekistan, 18 children died as a result of cough syrup prepared in India. In September 2006, in Panama City, Panama, a surprising number of patients with limb weakness and acute kidney injury was admitted, where investigation found that the illness was due to consumption of a locally made sugarless cough syrup [10]. These cases have shaken public confidence and cast serious doubt on the integrity of medicine manufacturers and distributors worldwide.

This paper examines the prevalence and risks associated with Cough Syrup adulteration and contamination and therefore emphasizes the critical role of rigorous testing, supply chain transparency, and strict regulatory enforcement (i.e need of pharmacovigilance with the purview of Forensic Science) to ensure drug safety and prevent recurrence of such public health disasters.

Methodology

This review aims to systematically analyse existing literature on Cough syrup, which requires pharmacovigilance. This article dealt with a detailed discussion of reaction mechanisms of cough syrups, various drugs involved, common adulterant-contaminants and their Forensic analysis. Further the article aims to provide data and case studies, where cough syrup has taken death trolls. To identify relevant literature, a comprehensive search was conducted across multiple databases over Google Scholar, Scopus, PubMed, etc. The initial search retrieved 95 articles. After removing duplicates 55 papers were used for review. Articles were assessed based on relevance to the research topic. Eligible studies were reviewed in detail to ensure alignment with inclusion criteria. To ensure the reliability of the selected literature, a quality assessment was conducted using PRISMA. The data were analysed using narrative synthesis. Key findings were compared to identify patterns, contrasts, and gaps in the literature. This review is subject to certain limitations were potential exclusion of unpublished studies or non-English publications, subjectivity in interpreting and synthesizing findings and variability in the methodological quality of included studies.

History of Cough Syrups

The existence of cough syrups goes beyond a millennium with no evidence found of any one physician being responsible for their introduction. While the concept of cough syrups began in Europe, especially in Germany, the origin and inspiration of treating cough symptoms with syrup-like remedies came from ancient Asian herbal practices with roots from sugarcane plantations in Bengal used in the production of sugar used in the synthesis process of cough syrups [1]. Sugar, was manufactured from sugar-cane in Bengal,

which was called sharkara, a Sanskrit word which meant a substance made up of small grains. Cough syrups have been found to have been made in various countries before the 18th century e.g in Egypt (1000BC) where natural syrups made from honey were made to suppress coughs and clear respiratory tracts, in India where ayurvedic medicines were used to treat coughs with natural plant based substances, and in Ancient China (1600) where natural remedies like Nin Jiom Pei PaKoa, a Chinese cough syrup were used but were never recognized world-wide as they were never mass produced. The later history of cough syrups was distinctly noted back in the 19th century where use of opium poppy plant-based substances like morphine and heroin were used to manufacture cough syrups. The first cough syrup to be chemically synthesised was Heroin which was supposed to be a safer alternative to morphine, but then proved to be even more potent. This cough syrup was synthesised by Felix Hoffman, a chemist from Bayer Pharmaceuticals in Germany. Prospan, a cough syrup later manufactured in Germany in the 1950s, then became famous for its effective and well-tolerated qualities in both adults and children over 2 years of age and has been recognized globally for its reliability till date [1,11]. Since then, chemists have been dedicated to synthesizing more cough syrups with less side effects and minimal risks of fatigue, drowsiness, and addiction using modern medicine and improved analysis techniques. Some of these early syrups are still used to date, but these are safer and have been proven to have less side effects. Some brands are: 4Cs, Choats, Benylin, Woods, Covonia,Vicks Vapodrops, Dabur Honitus, Baidhyanath, Kasamrit, Astha Kind DX, Benadryl, Tixylix, Torex, Rexcof and they commonly use ingredients like dextromethorphan, guaifenesin, iodine, diphenhydramine, promethazine, ambroxol, and bromhexine as their active ingredients. Cough syrups are widely used in the developing world, and they have been developing ever since being first discovered. Table 1 gives a few examples of notable cough syrups across history.

Cough Syrup	Origin / Manufacturer	Key Ingredients	Period of Introduction
Nin Jiom Pei Pa Koa	China	Traditional herbal formulation containing loquat leaf, honey, herbs; used for cough and sore throat	~400 years ago (Traditional Chinese Medicine)
Heroin Cough Syrup	Bayer, Germany	Diacetylmorphine (Heroin); marketed as a non-addictive alternative to morphine	Late 1890s
Prospan	Germany	Ivy leaf extract (Hedera helix); herbal expectorant used for productive cough	1950s
Robitussin	USA	Dextromethorphan and/or Guaifenesin; widely used OTC cough suppressant/expectorant	1950s
Coricidin HBP (DXM)	USA	Dextromethorphan; formulated for high-blood-pressure patients (no decongestants)	Modern OTC
Cheratussin DAC	USA	Contains Codeine, Guaifenesin; prescription antitussive and expectorant	Modern prescription
Rite Aid Cough Syrup	USA	Often contains DXM or Guaifenesin depending on the version	Modern OTC
Zarbee's Naturals Cough Syrup	USA	Honey-based, herbal ingredients; no drugs like DXM	2000s
Safetussin	USA	Dextromethorphan formulations designed for safe use with other medications	Modern OTC
Vicks DayQuil Cough	USA	Dextromethorphan; non-drowsy formula	Modern OTC
Benylin	UK/Global	Contains Diphenhydramine, DXM, or Guaifenesin depending on variant	Mid-20th century onwards

Table 1 : Notable Cough Syrups across the History.

Cough Syrups and its Medical Aspect

Cough Physiology: Cough is a protective reflex; its purpose is expulsion of respiratory secretions and foreign particles from air passages. It occurs due to stimulation of mechano or chemoreceptor in throat and respiratory passages or stretch receptors in lungs. Cough is often a clue to the presence of respiratory disease.

Cough Mechanism: Spontaneous cough is triggered by stimulation of sensory nerve endings that are thought to be primarily rapidly adapting receptors and C fibers. Both chemical (e.g., capsaicin) and mechanical (eg, particulate in air pollution) stimuli may initiate the cough reflex. A cationic ion channel—the transient receptor potential vanilloid 1 (TRPV1)-found on rapidly adapting receptors and C fibers is the receptor for capsaicin and its expression is increased in patients with chronic cough. Afferent nerve endings richly innervate the pharynx, larynx, and airways to level of the terminal bronchioles and extend into the lung parenchina They may also be located in the external auditory meatus (the aurica-branch of the vagus nerve, or Arnold's nerve) and in the esophagus. Sensory signals travel via the vagus and superior laryngeal nerves to a region of the brainstem in the nucleus tractus solitarius vaguely identified as the "cough center." The cough reflex involves a highly orchestrated series of involuntary muscular actions, with the potential for input from cortical pathways as well. The vocal cords adduct, leading to transient upper-airway occlusion. Expiratory muscles contract, generating positive intrathoracic pressures which is as high as 300 mmhg. With sudden release of the laryngeal contraction, rapid expiratory flows are generated, exceeding the normal "envelope" of maximal expiration flow. Bronchial smooth muscle contraction together with dynamic compression of airway narrows airway lumens and maximizes the velocity of exhalation. The kinetic energy available to dislodge mucus from the inside of airway walls is directly proportional to the square of the velocity of expiratory airflow. A deep breath preceding a cough optimizes the function of the expiratory muscles; a series of repetitive coughs at successively lower lung volumes sweeps the point of maximal expiratory velocity progressively further into the lung periphery.

Common Treatment Approaches for Cough

Non Pharmacological Management

- Humidification.
- Steam inhalation.
- Gargle with lukewarm and salt water.
- Normal saline nasal irrigation
- Breathing techniques- Diaphragmatic or pursed lip breathing can be beneficial.
- Smoke cessation.
- Honey, Ginger & Lemon combination.

Pharmacological Management: Drugs for Cough

- **Pharyngeal Demulcents**: They soothe the throat and reduce afferent impulse from inflamed or irritated pharyngeal mucosa thus provide symptomatic relief in dry cough arising from throat. They includes- Lozenges, syrups, Liquorice

Expectorants (Mucokinetics)

- **Secretion enhancers:** Mechanism of action: They cause gastric irritation which leads to reflex irritation of bronchi as a result there is gradual clearance of secretion from the respiratory tract. eg- GUAIFENESIN (only FDA approved expectorant). Other expectorants- Iodides, Hypertonic saline (non-FDA approved).
- **Mucolytics**: Mechanism of action- They break down mucus, liquify it and facilitate removal. Mucolytics are especially useful in patients with tracheostomy, bronchitis, cystic fibrosis, etc. who have thick tenacious sputum or mucus plugs.
- **Bromohexine & Ambroxol**: A derivative of alkaloid vascine, is a mucolytic capable of inducing thin copious bronchial secretion. MOA- They depolymerise mucopolysaccharides directly as well as liberating lysosomal enzymes- network of fibres in tenacious sputum is broken. Rhinorrhoea and lacrimation, nausea, gastric irritation, hypersensitivity are common side effects.
- **N-Acetyl Cysteine, Methyl & Ethyl Cysteine**: They have sulfhydryl group which breaks disulphide bond in mucoproteins present in sputum and makes it less viscid. They can be administered orally as well as by inhalation of 10-20% of nebulised solution.
- **Carbocisteine:** It increases the production of sialomucins which liquifies mucus. It may break the gastric mucus barrier, therefore is contraindicated in Peptic Ulcer Disease. It can cause gastric discomfort and rashes. It is available in combination of Amoxicillin and Cephalexin for Bronchitis, Bronchiectasis, Sinusitis etc management.
- **DNAse:** They are used in Cystic Fibrosis.

Antitussive: These are drugs that act in the CNS to raise the threshold of the cough centre or act peripherally in the respiratory tract to reduce tussal impulses, or both these actions. Because they aim to control rather than eliminate cough, antitussives should be used only for Dry, non-productive cough or if it disturbs sleep or is hazardous (hernia, cardiac disease, piles, ocular surgery).

Central Antitussives

Opioids

- **Codeine(DrugofChoice),Pholcodine,Ethylmorphine**- They are used for mild to moderate cough.
- **Morphine, Methadone:** They are used for severe coughs. eg- Bronchial Cancer. Side effect- Constipation (least with ETHYLMORPHINE). Morphine is contraindicated in asthmatics and in patients with diminished respiratory reserve. They have maximum abuse potential.

Non-Opioids

- **Dextromethorphan:** A synthetic central NMDA (N methyl D aspartate) receptor antagonist; the d-isomer

has antitussive action while l-isomer is analgesic. It doesn't depress mucociliary function of the airway mucosa and is practically devoid of constipating action. Side effects- Dizziness, nausea, drowsiness; at high dose hallucinations and ataxia can occur.

- **Noscapine**: It depresses cough but has no narcotic, analgesic or dependence inducing properties. It's especially useful in Spasmodiac Cough. It can release histamine and produce bronchoconstriction in asthmatics.

Peripheral Antitussives

- **Local Anesthetics**: They inhibit stretch receptors. Eg- Lidocaine, Bupivacaine, Mexiletine.
- **Moguisteine:** They open K+ channels in peripheral nerves, which inhibits action potential for cough reflex.
- **Cromolyn**: They cause persistent depolarisation which inhibits cough impulses reaching the brain. Peripheral antitussives act on the lung.

Antihistamines: Many H1 antihistamines have been conventionally added to antitussives/expectorant formulations. They afford relief in cough due to their sedative and anticholinergic actions, but lack selectivity for cough centers. They have been specially promoted for cough in respiratory allergic states. Eg- Bilastine, Fexofenadine, Levocetrizine, Chlorpheniramine, Diphenhydramine etc.

Adulterant and Contaminants in Cough Syrup

Excipients are usually the non-active parts of a pharmaceutical formulation. While their main job in most medications is to help deliver and stabilize the active compound, in cough preparations they often have more complex and important roles. Over hundreds of excipients are present among them, excipients can be divided into: sweeteners, thickeners, flavors, colors, antimicrobials, and buffers. But this doesn't limit to only excipients in the cough syrups. With the increase in cases of adulteration and contamination, pharmaceutical contamination may result from mislabeling, unintentional production mistakes, or manufacturers intentionally contaminating the product for economic gain. Adulteration of excipients involves the intentional or accidental substitution, dilution, or contamination of inactive ingredients used in pharmaceutical formulations. Table 2 gives the list of adulterant and contaminant cough syrup.

Adulterants	Contaminants
Thickener (EG/ DEG)	Nitrosamine Impurities
Synthetic dyes	Heavy metals: Pb, Cd, As, Hg
Unapproved drugs: • Opioids: Codeine, Heroin, Morphine, Dextromethorphan • Non-opioids: Corticosteroids, Benzonates, Pseudoephidrine	Residual solvent: Methanol, Chloroform
	Microbial contaminants: Salmonella spp., Staphylococcus aureus, Escherichia coli, and Klebsiella pneumoniae, etc.

Table 2: List of Adulterants and Contaminants.

Adulterant

Thickener: Diethylene Glycol and Ethylene Glycol: In cough syrups, excipients like glycerol, propylene glycol, and sorbitol are crucial for providing viscosity, sweetness, and stability. However, several incidents have shown that these excipients can be tainted with toxic industrial chemicals like DEG and EG. These compounds, used in antifreeze and industrial solvents, can cause serious harm to the kidneys and liver when ingested [12-17]. However, ingesting them has been connected to nephrotoxicity and death. In pharmaceutical formulations, it primarily serves as a solvent or co-solvent. It is a safer pharmaceutical-grade solvent usually used to dissolve active ingredients in cough syrups. Oral solutions typically contain between 10% and 25% propylene glycol as an excipient [18-25]. However, as Diethylene glycol and ethylene glycol are cheaper, some manufacturers illegally use them as a substitute for propylene glycol to reduce production costs. Economic factors, such as the lower price of DEG compared to pharmaceutical-grade glycerol, have led to its illegal use in cough syrups, causing mass poisoning outbreaks in various countries. This kind of adulteration not only puts drug safety at risk but also reveals problems in verifying raw materials and regulatory control in pharmaceutical supply chains. To avoid future incidents, it is vital to ensure the purity and quality of excipients through strict testing and following Good Manufacturing Practices (GMP) [15].

Synthetic Dyes: Cough syrups have colouring agents to increase the palatability to the children and many adults. Caramel and anthocyanin dyes are mostly used dyes derived

naturally from plant sources or are available in nature. Whereas, dyes such as Sunset yellow, Ponceau 4R, Quinolone yellow, Carmoisine E122, Armaranth E123, and Patent blue V are synthetic. These synthetic dyes are possible causative agents of urticaria, hypersensitivity, etc. Yet, the use of synthetic dyes is more in the pharmaceutical industry as natural dyes are often unstable and their power to impart colour is lesser than synthetic dyes, thus to make syrup more appealing and considering placebo effect. Many find a relationship between the color and the effect of cough syrup i.e placebo effect, although there has been no established research for the same [23]. Brilliant Blue FCF, a synthetic coloring ingredient, was present in one of the examined syrups authorized by Ukraine, the FDA has approved this coloring agent but particularly in children, it may result in hyperkinetic activity and hypersensitivity [21].

The WHO typically advises against using coloring compounds in pediatric medications, particularly for young children and newborns. According to EMA, each coloring agent's usage must be adequately justified in terms of its potential to cause allergies and its low toxicological effects on the intended age group. These regulations stem from long-standing worries about the safety of synthetic coloring chemicals [22]. The concentration of dye or colouring agents should be between 0.0005% and 0.001% in liquid preparation like syrups [24,25].

Unapproved Active Drugs: **Opioid:** Codeine suppresses cough via its action on cough receptors in the central nervous system. In 2015 the European Medicine Agency released a statement that codeine containing cough syrups or medicine shall not be used on children under 12 years of age due to the possibility of severe adverse effects, such as breathing difficulties. Codeine is not advised for children and teenagers between the ages of 12 and 18 who have breathing issues since codeine may make this population more vulnerable to breathing issues. Patients of all ages who are "ultra-rapid metabolisers," who quickly metabolize codeine into morphine, should avoid using codeine for colds and coughs since they are more likely to experience severe adverse effects. Codeine should not be taken by nursing mothers since it can affect the infant through breast milk. The hepatic p450 system converts codeine to morphine at a variable and unpredictable rate. Patients who are CYP2D6, ultra-rapid metabolizers can generate a potentially fatal dose of morphine, while those without CYP2D6 function will not convert codeine to morphine [26-30].

The German pharmaceutical company Bayer introduced "Heroin" which was marketed as a cough syrup in 1895. It may seem unbelievable, but it was promoted as a non-addictive, safer substitute for morphine in the treatment of coughs. The Harrison Narcotics Act of 1914 outlawed heroin from over-the-counter cough syrups, and the Heroin Act of 1924 completely prohibited its use in medicine in the United States. The FDA discouraged the use of morphine by the middle of the 20th century due to the risk of overdose and dependence, but it remained in some prescription cough mixes for a longer period of time. It was eventually supplanted by safer non-opioid antitussives, such as dextromethorphan.

Dextromethorphan is commonly found over the counter medicine, which doesn't have analgesic effects and doesn't cause respiratory depression like codeine, although they are related. However, at large doses, the metabolite of dextromethorphan can induce euphoria, dysphoria, and hallucinations by inhibiting N-methyl-D-aspartate receptors. These effects resemble those of ketamine or phencyclidine. Dextromethorphan may therefore be abused [26]. Nausea, vomiting, lightheadedness, ataxia, lethargy, slurred speech, nystagmus, urine retention, hysteria, stupor, and coma are other adverse consequences of dextromethorphan [27]. Some strong long-term users of dextromethorphan experience bromism due to the hydrobromide salt formulation, which causes delirium, convulsions, and psychosis. High dosages of dextromethorphan or its interactions with other drugs, such as selective serotonin uptake inhibitors, can also cause serotonin syndrome.

Promethazine-codeine is a cough syrup that requires a prescription, although promethazine is antihistamine. Some people abuse this cough syrup mixture by combining it with alcohol or taking it with other drugs.

Non-Opioids: Corticosteroids may suppress cough by inhibiting airway inflammation and hyper-reactivity, however it is not commonly used in cough syrup [30], but is incorporated in oral syrups that require a prescription (such as prednisolone) to treat severe coughs brought on by inflammatory diseases including asthma, COPD, or post-infectious cough. They are frequently used for a brief "burst" of treatment because they reduce inflammation and edema of the airways.

Benzonatate, previously sold under the trade name of Tessalon, was approved by the FDA in 1958 as a prescription antitussive in patients. Chemically related to procaine, benzonatate is an oral anesthetic that is thought to control coughing by blocking pulmonary stretch receptors [31,32]. The FDA issued a safety alert in December 2010 on the possibility that children under the age of ten could die if they accidentally consumed benzonatate. Children under the age of two have reportedly died after taking as few as one or two benzonatate tablets. Overdose symptoms include tremors, seizures, restlessness, and coma. After consumption, symptoms usually appear 15 to 20 minutes later, and death can happen within hours. The potential for abuse is less.

Pseudoephedrine mainly operates as an α-adrenergic receptor agonist, causing vasoconstriction in the nasal mucosa and decreasing post-nasal drip and airway edema, which may indirectly alleviate cough symptoms. Pseudoephedrine can produce dose-related cardiovascular and central nervous system toxicity, including hypertension, tachycardia, sleeplessness, agitation, and, in rare instances, arrhythmias or ischemic events due to excessive adrenergic stimulation, even though it is usually safe at therapeutic levels. Under the Combat Methamphetamine Epidemic Act (CMEA) of 2005, the U.S. FDA established stringent control measures requiring dispensing, identification checks, purchase limits, and record-keeping for products containing pseudoephedrine because it is also a precursor used in the illegal and clandestine synthesis of methamphetamine.

Contaminant

Contamination of cough syrup is a significant public health issue since these over-the-counter drugs are widely consumed and can harbor toxic impurities added during production, packaging, or storage. Some of the common impurities found in cough syrup are heavy metals (e.g., lead, cadmium, chromium, and nickel), nitrosamines (e.g., NDMA and NDEA), toxic solvents, and occasionally microbial agents. Heavy metals are introduced by using contaminated raw materials or equipment and can lead to neurological, renal, and developmental disorders with long-term exposure. Nitrosamines, which are derived from chemical transformations of amines and nitrites, are potential human carcinogens that can be present even at trace levels. Tainted syrup reports have resulted in severe cases of poisoning, thereby highlighting the importance of meticulous quality control, good manufacturing practices (GMP), and rigorous regulatory surveillance to safeguard product quality and the consumer, especially children, who are more susceptible to toxicity effects.

Nitrosamine Impurities: Taylor P, et al. [33] determined N-nitrosodimethylamine (NDMA) and N-nitrosodiethylamine (NDEA) in cough/cold medication and antihistamines employing gas–liquid chromatography–thermal energy analysis. NDMA and NDEA were found in all antihistamine tablets (0.22–3.6 μg/kg and 0.35–2.7 μg/kg, respectively), whereas there was one trace of NDMA content in a cough syrup (0.05 μg/kg). It was concluded by the research that while contamination in syrups was low, nitrosamines might form in vivo from drugs containing amines, and monitoring of such impurities should be continued. Aggarwal P, et al. [34] established a sensitive analytical technique to quantitate nitrosamine impurities in antitussive cough syrups by applying SPE followed by GC–MS. The analysis was focused on small-molecule nitrosamines, such as NDMA, NDEA, NMOR, NDIPA, and NIPEA, which have been characterized as likely human carcinogens. Findings indicated that nitrosamine residues are possible at trace levels in cough syrups and emphasize the necessity of regular screening and rigorous regulation to avoid consumer exposure to these carcinogenic contaminants.

Heavy Metals: Several heavy metals, particularly lead, cadmium, chromium, and nickel, were detected at levels exceeding international safety limits in the commonly abused cough syrups tested in Sokoto, Nigeria [35]. Chronic consumption increases the risk of heavy metal accumulation and toxicity. Long-term effects of heavy metal exposure include memory loss, cognitive decline, neurotoxicity and hepatic problems, developmental and reproductive toxicity, damage to DNA and possible carcinogenicity. Although heavy metals shouldn't be present in medications, they can be detected in cough syrups because of intentional additions, impurities or pollution. It was also found that most of the cough syrup samples in Awka, Anambra State, Nigeria that were examined had detectable levels of these hazardous metals, with cadmium levels up to 2.45 mg/L and lead levels up to 1.08 mg/L [36]. Children are more susceptible to heavy metal toxicity, including renal impairment and neurodevelopmental deficits. Several herbal cough syrups sold in the United Arab Emirates contain lead, cadmium, chromium, and arsenic, some of which are above advised safety limits. A number of factors, including the source of raw materials, environmental contamination, and insufficient manufacturing controls, were blamed for the contamination [37]. Olutona GO, te al. [38] evaluated the levels of lead, cadmium, and manganese in pediatric over-the-counter (OTC) drugs made in Uganda. Twelve brands of pediatric syrups, including antihistamines, cough expectorants, antipyretics, and cold/flu preparations gathered from Kampala pharmacies, were examined using Flame Atomic Absorption Spectroscopy (FAAS AAnalyst 400) following acid digestion. All samples had detectable levels of lead and cadmium, according to the results; antihistamines had the highest lead concentration (7.01 μg/mL), while manganese was not found in any of the formulations. Saeed M, et. al. [39] examined Pakistani herbal medicinal preparations for respiratory infections and detected levels of lead, cadmium, arsenic, and mercury in all samples by atomic absorption spectrophotometry. Lead content was up to 277.44 μg/day and cadmium up to 10.99 μg/day which is beyond safety standards, which can cause severe health hazards.

Residual solvents – Methanol and Chloroform: A Vadodara-based facility produced the methanol-tainted "herbal syrup" that caused numerous fatalities in Gujarat's Kheda district. Investigations revealed that it was manufactured using leftover sanitizer stock and industrial methanol, then misrepresented as a herbal remedy. Charges

of culpable homicide, adulteration, and forgery resulted from the case, which was connected to previously flagged illegal producers and exposed significant regulatory shortcomings in the monitoring of chemical and drug safety [40]. Methanol can result in visual abnormalities, metabolic acidosis, and poisoning. Strict testing is advised by regulatory bodies to guarantee that any residual methanol stays within acceptable bounds.

Chloroform were constituent of a number of proprietary cough linetuses, some of which were available in Australia even without a prescription [41], but chloroform had been banned in 1976 by the FDA. Chloroform was found as an additive in one traditional herbal cough medicine [42]. Traditional cough syrups like Kimball White Pine and Tar Cough Syrup included chloroform as a remedy for coughing. It was historically used for its numbing effects, but it has mostly been phased out of modern products due to its high toxicity and risk of cancer. Chloroform contaminant or residues, can lead to liver damage, kidney damage, and a higher chance of developing cancer. Current laws closely regulate acceptable leftover levels, making its presence in medicines uncommon and strictly monitored.

Microbial Contamination: Bacterial contamination in retailed cough syrup is a serious public health concern in developing nations, where product safety is jeopardized by poor hygiene, insufficient regulation, and inappropriate storage [43]. According to studies, harmful microorganisms like Salmonella spp., Staphylococcus aureus, Escherichia coli, and Klebsiella pneumoniae are commonly found in oral syrups sold in open markets [44]. These microorganisms can lead to both systemic and gastrointestinal infections. The use of non-sterile water, poor manufacturing techniques, and unsanitary handling in retail settings are frequently blamed for the contamination [45,46]. According to a recent Wukari investigation, a number of retailed syrups had microbial loads above the threshold, indicating inadequate quality control and exposure to environmental pollutants [47,48]. Osuntokun OT, et al. [49] examined the presence of microorganisms in cough syrups at patent medicine stores in Akungba-Akoko, Nigeria, isolated and identified a number of bacterial contaminants, such as Klebsiella spp., E. coli, and S. aureus, using conventional microbiological techniques. These pathogens' presence suggested inadequate manufacturing or storage procedures as well as poor hygiene. AbuTaha AS, et al. [48] examined the growth of S. aureus, E. coli, P. aeruginosa, and C. albicans in five distinct cough syrups, where compared to imported cough syrups, locally produced cough syrups were more susceptible to microbial contamination, indicating the need for improved GMP and packaging procedures. There is the necessity of regular microbial screening, stringent regulatory oversight, and public awareness campaigns [49].

Forensic Analysis

Gas Chromatography

GC coupled with FID is a very useful tool in determining presence of EG, DEG and PEG. U.S. Pharmacopeia provides a procedure to determine the concentration of residual EG, DEG, and TEG in ethoxylated products. Samples are prepared by dissolving the substance in acetone and adding butane-1,3-diol as an internal standard. Calibration uses standard solutions with known concentrations of EG, DEG, and TEG.

Chromatographic separation can be done on a 0.53-mm × 30-m capillary column coated with a G3 phase, with carrier gas Helium has 5 mL/min flowrate. A programmed temperature gradient is used to resolve the glycols effectively, where injector temperature is 270 °C and detector temperature is 290 °C. The relative retention time can be obtained; quantification depends on comparing peak response ratios of each glycol to the internal standard in both sample and standard preparations. A standard calculation is used to report results in micrograms per gram. Mass spectrometry coupled with GC can sensitively detect and quantify contaminants such as EG, DEG, and nitrosamine impurities at very low levels (ng/mL). In this technique, the samples are separated and then subjected to mass analysis [50].

In accordance with USP, residual solvents are usually measured using headspace GC–FID or headspace GC–MS. By aliquoting a known weight or volume, diluting to a specified volume or adding a headspace diluent such as water, saline, or an appropriate solvent, equilibrating temperature/time, and analyzing using verified headspace conditions and calibrated standards. Class-1 (like chloroform) and Class-2 (like methanol) solvents have strict limits in accordance with USP [51].

Liquid Chromatography

As low-level contaminants, nitrosamines are strong genotoxic carcinogens. Highly sensitive, verified procedures (LOQs in low ng/g or ng/mL) are expected by regulatory agencies. The current standard for nitrosamine screening and quantitation in pharmaceuticals and finished products is LC coupled to high-resolution MS (LC-HRMS) or LC–MS/MS due to its sensitivity and selectivity; sample preparation typically involves dilution followed by SPE (solid-phase extraction) clean-up or QuEChERS-style cleanup to remove matrix components. HPLC-HRMS with ESI and APCI conjugation was utilised by US-FDA to determine nitrosamines in pharmaceuticals products [52].

Because of its superior sensitivity, selectivity, and multiplexing capacity, LC–MS/MS is typically used to screen for unapproved active drugs (such as codeine, morphine, oxycodone, tramadol, or non-opioid Active Pharmaceutical Ingredients). A typical approach consists of two steps: broad-scope screening with LC-MS/MS (either full-scan HRMS for unknowns or targeted MRM libraries for known suspects), and confirmatory quantification using a validated targeted LC-MS/MS assay against certified reference standards. For syrups, sample preparation typically involves protein precipitation and simple dilution, or SPE for concentrating low-level activities and eliminating excipients [53].

Inductively Coupled Plasma

To measure the elemental contamination ICP or ICP-OES can be used. ICP-OES for elements with higher concentration or ICP-MS, used for ultra-trace detection of several elements. For ICP analysis, sample preparation necessitates the closed-vessel microwave acid digestion of an aliquot of the syrup to obtain heavy metals; technique validation comprises recovery from matrix, limits of detection/quantitation, and contamination control. Cd, Pb are regulated and limited to 5 μg/day and 15 μg/day for As in oral dosage like in cough syrup by ICH Harmonised Guidelines [54].

Microbial Analysis

Oral liquids that are not sterile must adhere to microbiological quality standards. Culture-based techniques (plate counts, membrane filtration, enrichment) are used for standard pharmacopoeial microbial enumeration (total aerobic microbial count, total yeast and mold counts) and specific pathogen tests (e.g., Salmonella, E. coli, P. aeruginosa, S. aureus). ATP bioluminescence, lateral flow, or PCR/qPCR assays may be employed as adjuncts for quick screening or environmental monitoring [55].

Forensic Pharmacovigilance

Forensic pharmacology answers questions regarding the connection between chemicals and an individual's behavior, disease, harm, or demise. It can be characterized as the interpretation of the duration of action and effects of medications to aid in the medico-legal process. The application of standard pharmacovigilance methods for registration, analysis, and investigation in order to detect harm in the form of adverse medication reactions brought on by counterfeit, inferior pharmaceutical products is known as forensic pharmacovigilance. Drug safety for patients is very important, in an effort to safeguard patient safety, pharmacovigilance is required to keep a close eye on the pattern of adverse events brought by drug use. The number of medicolegal cases has increased in recent years where many criminal and civil cases require cooperation between pharmacovigilance and forensic sciences.

It is common to confuse a forensic pharmacologist with a forensic toxicologist. Compared to a forensic toxicologist, who is also involved in drug testing and providing testimony for attorneys in criminal cases, a forensic pharmacologist is involved in forensics much more broadly including but not limiting to adverse drug reactions, drug overdoses, drug interactions, personal harm from medication exposure, effects from drug abuse or industrial chemicals, and chemical-induced cancer are just a few of the many issues that fall under his area of expertise.

With recent increase in cases of cough syrup adulteration and contamination, taking death tolls, it is required to spread awareness, have robust regulatory frameworks to protect public health and prevent future incidents, as well as there is need of Forensic pharmacovigilance. Forensic pharmacovigilance is required to understand the deaths caused by such medications [56].

Case Studies

- **Panama (2006):** There was an official estimate of 78 deaths resulting from unexplained renal failure with neurological dysfunction. Later, on investigation it was found that contaminated cough syrup with an average of 8.1% DEG caused such deaths. The syrup was manufactured in India imported from China through a European broker where cough syrup was found to be contaminated with an average of 22.2% DEGs.
- **Uzbekistan, Gambia and Indonesia (2022-2023):** In 2022, more than 300 children -mainly aged under 5 in Gambia, Indonesia, and Uzbekistan died of acute kidney injury, associated with contaminated over-the-counter cough syrups that had high levels of DEG and EG. The FDA issued a warning detailing the potentially fatal consequences of the cough syrups, including discomfort, vomiting, diarrhea, painful micturition, headache, changed mental state, and severe renal damage. The WHO sent alerts asking to remove cough syrups made by India's Maiden Pharmaceuticals and Marion Biotech, which are linked with deaths in Gambia and Uzbekistan respectively.
- **Cameroon (July, 2023):** The WHO sent an alert on a batch of substandard cough syrup found in Cameroon, which had high levels of DEG. The incident involving Naturcold syrup was first reported on March 13, 2023. It was listed on the product packaging as Franken International, England which the UK national regulatory authority confirmed as non-existent in the UK. Since the stated manufacturer is unknown, WHO did not provided on the safety and quality of these products. WHO

medical product alert was issued on four substandard products- Promethazine oral solution, Kofexmalin baby cough syrup, Makoff baby cough Syrup, and Magrip N Cold Syrup.

- **Liberia**: The Nigerian regulator and the Liberian health regulator identified contaminated syrups made by India's Synercare Mumbai in Liberia.
- **Micronesia and Marshall Islands (2023, April)**: In April 2023, the WHO found that another Indian drugmaker had exported contaminated cough syrup to these countries.
- **Iraq (2023, August):** In August 2023, the WHO issued an alert for a batch of "COLD OUT" syrup made by Fourrts Laboratories sold in Iraq, which had unacceptable levels of DEG and EG.
- **India (2025):** Indian health officials confirmed that 17 children under the age of 5 died after consuming cough syrup found to contain DEG at levels nearly 500 times higher than the permissible limit. Deaths occurred in different regions of India. Laboratory testing identified the contaminated product as "Coldrif", a locally manufactured cough syrup brand. Indian authorities officially banned the sale and distribution of Coldrif and revoked the license of Sresan Pharmaceuticals after toxicology results confirmed the presence of DEG. The FDA confirmed that the cough syrup had not been sold outside India.

Country	Year	Adulterant/ Contaminant	Number of deaths
USA	1937	DEG	>100
Bangladesh	1990-1992	DEG	236
Haiti	Mid 2000s	DEG	60
Panama	2006	DEG	78
Gambia	2022	DEG and EG	About 70
Nigeria	2022	DEG	84
Indonesia	2022-2023	DEG	144
Uzbekistan	2022-2023	EG	20
Cameroon	2023	DEG	12
Iraq	2023	DEG and EG	-
Cambodia	2023	DEG and EG	None reported
USA	2025	Bacillus cereus	-
India	2025 and ongoing	DEG and EG	23

Table 3: Statistics of Case Studies.

Conclusion

Cough syrups which have long been relied upon as commonplace treatments for respiratory discomfort. Recent tragedies connected to ethylene glycol (EG) and diethylene glycol (DEG) poisoning highlight the ongoing vulnerabilities that exist within global drug manufacturing and supply chains, despite the fact that modern pharmaceutical advancements have enhanced their safety and efficacy. The recent events in India, The Gambia, Uzbekistan, and Panama serve as sobering reminders that even commonly used drugs like cough syrup have the potential to be lethal when ethical production procedures, quality control, and regulatory supervision are compromised. With recurrence of cases of contamination, there is need of rigorous analytical testing, greater transparency in sourcing and supply chains, and unwavering adherence to regulatory standards. Such rigorous analysis shall be taken into the purview of pharmacovigilance and providing justice to the victims affected is a part of Forensic Science. Averting such public health catastrophes necessitates a shared commitment: global health organizations must continue to be watchful, manufacturers must maintain stringent quality standards, and regulators must enforce compliance without compromise. Hence, Forensic Pharmacovigilance is required to the coming era, where the analysis of adulterants and contaminants fall under the purview of Forensic Science and not just the role of Pharmaceuticals.

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