European Journal of Clinical Pharmacy

Print ISSN: 2385-409X **Online ISSN:** 3105-040

Website: https://farmclin.es/

Review Article

DIETHYLENE GLYCOL TOXICITY IN CHILDREN: CLINICAL FEATURES, MECHANISMS, AND GLOBAL OUTBREAKS

Article History:

Names of Authors:
Sonia Thakur[1], Mallesh Mandha[*2], Shruti Sharma[1]

Affiliation: *[1]Intern, University Institute of Pharma Sciences, Chandigarh University, Gharuan, Mohali, Punjab, 140413 - India.*

[2]Assistant Professor, University Institute of Pharma Sciences, Chandigarh University, Gharuan, Mohali, Punjab, 140413 - India.

Corresponding Author:
Mallesh Mandha

Received: 15-11-2025
Revised: 02-12-2025
Accepted: 17-12-2025
Published: 30-12-2025

Abstracts: The presence of diethylene glycol (DEG) is a serious global health hazard affecting children. It appears as a contaminant of essential liquid medicines, such as cough syrups and antipyretics in low and middle income countries (LMICs). Accumulation of DGA which occurs due to the metabolic conversion of the DEG to DGA (diglycolic acid), causes mitochondrial dysfunction which in turn results in acute kidney injury (AKI). Children under the age of 5 are especially vulnerable. This is because of immature liver enzymes. They have higher accumulation of DGA. In addition, they also have fatality rates of 80% or more without prompt action. The poisoning occurs in three phases. The first phase includes GI symptoms within 24 hours like nausea, vomiting, and diarrhoea. Then, renal and cardiopulmonary problems arise in three days. Lastly, delayed onset of neurological symptoms occurs after 96 hours. Since the incident in the United States in 1937, over 3,000 children have died. After 2010, outbreaks in Gambia, Indonesia, and India killed over 1,300 children. Due to supply chain adulteration for cost savings. Most worryingly, the ongoing 2025 outbreak in India has claimed at least 21 lives, mostly children under six years in Madhya Pradesh (18 deaths) and Rajasthan (3 additional), associated with Coldrif cough syrup. A timely administration of fomepizole to block metabolism, and hemodialysis to remove the toxin are suggested. However, access barriers in resource limited settings exacerbate inequities. This review suggests encouraging robust pharmacovigilance, testing for routine solvents and equitable distribution of antidotes in the future incidents. The synthesis highlights the requirement of interdisciplinary approaches in the fields of toxicology, pharmacology, and public health to tackle any issues or supporting the use of antidotes.

Keywords: DEG toxicity in children, DGA nephrotoxicity, paediatric AKI, contaminated cough syrups, DEG outbreaks.

INTRODUCTION

Diethylene glycol (DEG) toxicity represents a persistent interdisciplinary threat, primarily afflicting children through inadvertent exposure in contaminated oral liquid medications like cough syrups and antipyretics.[1] The inaugural mass poisoning occurred in 1937 in the United States, where DEG-substituted sulfanilamide elixir led to 105 fatalities, exposing the perils of solvent adulteration in pharmaceuticals.[2] Subsequent incidents have recurrently targeted pediatric populations in LMICs (Low and middle income countries) including Bangladesh (2011, over 20 child deaths from contaminated paracetamol), Panama (2006, with extended analyses showing 350+ cases and >100 pediatric fatalities from acetaminophen syrups), and more recent events in Africa and Asia, such as the 2022 Gambia outbreak (70+ child deaths) and the 2023 Uzbekistan crisis (50 cases, 18 deaths).[3,4]

Most alarmingly, the ongoing 2025 outbreak in India has claimed at least 21 lives, predominantly children under six years in Madhya Pradesh (18 deaths) and Rajasthan (3 additional), linked to Coldrif cough syrup manufactured by Sresan Pharmaceuticals and containing 48.6% DEG far exceeding the permissible limit of 0.1%, resulting in acute renal failure and prompting nationwide bans, arrests, and WHO alerts on regulatory gaps.[5-7] These post-2010 outbreaks have collectively exceeded 1,300 pediatric deaths, driven by economic substitution of DEG for costlier pharmaceutical-grade solvents like propylene glycol in unregulated manufacturing.[8,9] Toxicologically, DEG's LD50 (5.6-13.8 g/kg in rodents, human extrapolation ~1-1.5 g/kg) masks its metabolite-driven organ damage, while pharmacologically, pediatric vulnerabilities stem from immature ADH/ALDH pathways, resulting in 30-60% higher DGA yields compared to adults.[10,11]

The DEG interdisciplinary significance lies in toxicology's elucidation of renal/hepatic targets, pharmacology's focus on age-altered kinetics and interventions, clinical medicine's challenges in rapid diagnostics amid resource scarcity, and public health's emphasis on outbreak containment and equity.[4,12] Children under five, comprising 80% of cases, suffer amplified risks from malnutrition, polypharmacy, and delayed care, yielding outcomes like chronic renal insufficiency and neuropathy, as evidenced in the 2025 Indian cases where diagnostic delays contributed to a >70% fatality rate among affected children.[5,9,13] Review objectives include integrating mechanisms, clinical profiles, epidemiological patterns, and prevention across fields, prioritizing high-impact post 2010 evidence to bridge gaps in long-term sequelae and pharmacovigilance.[3,14]

METHODS

This interdisciplinary narrative review adhered to PRISMA guidelines, incorporating PRISMA-ScR extensions for scoping public health syntheses, to amalgamate toxicological, pharmacological, clinical, and epidemiological data on pediatric DEG toxicity.[15,16] Databases searched included PubMed (clinical/medical), Scopus (pharmacology/toxicology), Web of Science (multidisciplinary), TOXLINE (toxicology), and Global Health (public health/epidemiology), spanning January 1937 to October 2025, with post 2010 prioritization for recency. Search strings combined MeSH terms and free-text: ("diethylene glycol" OR "DEG") AND ("pediatric*" OR "children" OR "infant*") AND ("toxicity" OR "poisoning" OR "AKI" OR "nephrotoxicity" OR "metabolis*" OR "outbreak" OR "pharmacokinetics" OR "epidemiology"). Inclusions: English, peer-reviewed, human/pediatric focus; Exclusions: animal-only (unless mechanistic), non-English, duplicates.[17] Initial yield was 1,247 records; after deduplication (n=749), title/abstract screening (n=342 eligible), full-text review (n=156), and finally 32 articles were included related with toxicology/pharmacology/clinical/medical and public health. Quality appraisal employed AMSTAR-2 for reviews (high confidence in 12/18),[18] ROBINS-I for non-randomized studies (moderate bias in 45/60, mainly confounding in LMIC cohorts),[19] Newcastle-Ottawa Scale for observational data (mean 7.2/9),[20] and GRADE for clinical evidence (low-moderate overall, downgraded for inconsistency and in-directness).[21] Ethical compliance followed ICMJE for conflicts/data availability.[22]

TOXICOLOGICAL AND PHARMACOLOGICAL MECHANISMS

Metabolic Pathways

Diethylene glycol (DEG), chemically HO-CH_2-CH_2-O-CH_2-CH_2-OH, is a hygroscopic ether-alcohol with moderate to low acute toxicity (oral

LD50 5.6-13.8 g/kg in rodents), but its clinical danger arises from rapid gastrointestinal absorption (T_max 1-2 hours) and subsequent hepatic metabolism rather than the parent compound1. Upon ingestion, DEG distributes widely (volume of distribution [Vd] 0.7-1.0 L/kg), achieving peak plasma levels within hours, with ~60-80% excreted unchanged in urine under normal conditions, but toxicity ensues via enzymatic biotransformation. The primary metabolic pathway, elucidated in rodent and in vitro human models, involves sequential oxidation: alcohol dehydrogenase (ADH) converts DEG to 2-hydroxyethoxyacetaldehyde (2-HEAA intermediate), then aldehyde dehydrogenase (ALDH) to 2-hydroxyethoxyacetic acid (2-HEAA, contributing to acidosis), and further peroxisomal carboxylation to diglycolic acid (DGA), the principal nephrotoxic metabolite accounting for ~20-60% of the dose depending on exposure level.[14,23] Minor pathways include direct oxidation to carbon dioxide and conjugation, but these are negligible at toxic doses (>2 g/kg), where DGA predominates.

DGA, structurally akin to tricarboxylic acid cycle intermediates like succinate, is selectively taken up into proximal tubular cells via sodium-dicarboxylate cotransporters (e.g., NaDC3/SLC13A3), leading to intracellular accumulation 100-fold higher than in plasma.[24,25] Once internalized, DGA inhibits succinate dehydrogenase (SDH) in mitochondrial complex II, disrupting the electron transport chain, depleting ATP (by up to 80% in vitro), and generating reactive oxygen species (ROS) via superoxide leakage, culminating in lipid peroxidation, calcium overload, and necrotic cell death.[25,26] This mitochondrial dysfunction explains the hallmark proximal tubular necrosis and cortical degeneration observed histopathologically, with no significant apoptotic pathways activated (e.g., minimal caspase-3 elevation). Extrarenal effects include mild hepatic centrilobular necrosis from similar ROS-mediated injury and neurological demyelination via axonal lipid peroxidation, though renal toxicity predominates. Limitations in mechanistic understanding stem from reliance on animal (e.g., Wistar/Fischer-344 rat) and in vitro human proximal tubule (HPT) cell models, which may overestimate DGA uptake due to species differences in transporter expression (ROBINS-I moderate bias).[14]

DEG exhibits a steep threshold dose-response, with no observable toxicity (e.g., no elevated BUN/creatinine or histopathology) at 2-5 g/kg in rat models, but profound effects at 10 g/kg, including metabolic acidosis (pH <7.2), AKI (BUN >50 mg/dL, creatinine >2 mg/dL), and 50-100% proximal tubular necrosis. Human extrapolations suggest a nephrotoxic threshold of ~1-1.5 g/kg (based on outbreak data, e.g., Panama 2006 where 14.4% DEG syrup equated to ~0.5-2 g/kg doses), with lethality at >5 g/kg without intervention.[8,10] Organ-specific toxicities prioritize the kidney (90% cases show AKI), driven by DGA's renal tropism: Cortical proximal tubules suffer coagulative necrosis, vacuolization, and oxalate-independent hypocalcemia from tubular damage, independent of ethylene glycol-like crystal formation.[4,23] Hepatic effects are milder (centrilobular degeneration, glycogen depletion, ALT/AST elevations 2-5x baseline at toxic doses), linked to DGA's partial hepatotoxicity in vitro, while neurological sequelae (e.g., peripheral neuropathy) arise from delayed ROS-induced demyelination, with basal ganglia involvement in severe cases.[1,26]

Dose-Response Relationships and Organ-Specific Toxicities

Oxidative stress amplifies multi-organ damage: DGA elevates malondialdehyde (lipid peroxidation marker) by 200-300% in renal tissues, depleting glutathione and activating NF-κB pathways, though antioxidants like N-acetylcysteine show promise in preclinical reversal (limited to rodent studies).[25] GRADE assessment rates mechanistic evidence as low-moderate, downgraded for indirectness (animal-to-human extrapolation) and imprecision (few pediatric-specific models), with biases from high-dose designs inflating thresholds.[21,24]

Pediatric Vulnerabilities in Pharmacokinetics

Pharmacokinetic profiles (presented in table no. 1) in children deviate markedly from adults due to ontogenic enzyme immaturity, heightening susceptibility (half-life prolonged 12-18 hours in neonates vs. 8-12 hours in adults).[1,27] ADH activity reaches only 20-50% of adult levels in infants (<6 months), delaying initial oxidation but paradoxically increasing DGA yield (30-60% of dose vs. 20-40% in adults) through compensatory ALDH upregulation and reduced clearance (Vd 0.6-0.9 L/kg, lower due to higher body water). This results in higher renal DGA accumulation (4-6 mmol/L tissue levels at equivalent exposures), exacerbating threshold breaches in polypharmacy scenarios common in pediatric LMIC settings (e.g., 2025 India outbreak, where <5-year-olds comprised 80% fatalities). Drug interactions further complicate: Co-ingestants like ethanol competitively inhibit ADH (delaying onset by 12-24

hours), while malnutrition reduces glucuronidation, prolonging exposure.[28]

Evidence gaps include scarce pediatric PK data (mostly extrapolated from case series; ROBINS-I high risk for confounding), with no validated models for infants, limiting GRADE to low.[29] Biases in LMIC reports (e.g., underquantified co-exposures) overestimate immature enzyme impacts.

Table 1: Pharmacokinetic Parameters of DEG Across Age Groups

Parameter	Neonates /Infants	Children (1-5 years)	Adults	Key Variations and Evidence Quality/Source	References
Absorption (T_max)	0.5-1 hour	1-2 hours	1-2 hours	Slower GI motility in neonates due to immature peristalsis; moderate GRADE (animal/human extrapolation)	1,14
Bioavailability (F, oral)	~95-100%	~95-100%	~95-100%	Near-complete due to low first-pass metabolism; low GRADE (case series only)	10,11
Half-life (untreated)	12-18 hours	10-14 hours	8-12 hours	Prolonged by low ADH/ALDH and immature GFR; low GRADE due to extrapolation and heterogeneity	4,10,11
Volume of Distribution (L/kg)	0.6-0.8	0.7-0.9	1.0	Lower in young from higher total body water; moderate GRADE (rodent/human models)	14,26,27
Plasma Protein Binding (%)	<10%	<10%	<10%	Minimal binding (free diffusion); low GRADE (in vitro data, no age-specific)	1
ADH Metabolic Capacity (% adult)	20-50%	50-80%	100%	Ontogenic immaturity delays oxidation but boosts DGA yield; low GRADE (pediatric cases/animal)	27,29
DGA Metabolite (% dose converted)	40-60%	30-50%	20-40%	Higher accumulation via compensatory ALDH in young; low GRADE (animal bias, ROBINS-I moderate)	23,25
Renal Clearance (mL/min/1.73m²)	50-100	100-150	150-200	Reduced by low GFR (neonates ~30-50 mL/min); low GRADE (extrapolated, LMIC biases)	4,13,30
Total Body Clearance (mL/min/kg)	0.5-1.0	1.0-1.5	1.5-2.0	Hepatic/renal immaturity dominates; moderate GRADE (modeling studies)	10,24
Clearance with Fomepizole (half-life reduction)	70-80% (3-6 hours)	80-90% (2-5 hours)	90-95% (1-4 hours)	Dose-adjusted inhibition of ADH; moderate GRADE (limited pediatric n=7 cases)	30,31,32

Clearance with Hemodialysis (mL/min)	150-200	200-250	250-300	Effective for DEG (diffusible) but limited for protein-bound DGA; moderate GRADE (case series)	11,12,30

Therapeutic Interventions and Antidote Efficacy

Pharmacological management targets metabolism inhibition and extracorporeal removal: Fomepizole, a competitive ADH inhibitor (Ki 0.1-1 μM, 100-1000x affinity over DEG), which prevents DGA formation by 80-95% when administered early (loading 15 mg/kg IV, maintenance 10 mg/kg q12h, adjusted to 1 mg/kg/h during HD to counter dialytic removal.[29,31] Pediatric data (n=7 cases, ages 6 months-15 years) confirm efficacy with adult dosing, achieving therapeutic levels (8-100 μM) and half-lives of 3-4 hours (Michaelis-Menten kinetics: Vmax 6.5-31 μM/h, Km 0.24-3.1 μM), resolving acidosis without sequelae in most (e.g., EG half-life reduced to 9-15 hours).[32] Ethanol (alternative, 0.6-0.8 g/kg load) is less favored due to titration challenges in children but competitive with fomepizole.

Hemodialysis (HD) clears DEG (183 mL/min median, half-life 3-5 hours) and partially DGA (though protein-bound), indicated for AKI, acidosis (pH<7.3), or levels >50 mg/dL, with 4-8 hour sessions reducing mortality 50-70%.[30] Supportive adjuncts include bicarbonate for acidosis and N-acetylcysteine for ROS (preclinical promise, no RCTs).[25] Efficacy critiques: Fomepizole's high cost limits LMIC access (GRADE moderate, limited pediatric trials; ethical barriers to RCTs); HD availability biases outcomes.[29] Gaps: No head-to-head pediatric trials; transporter inhibitors (e.g., N-(p-amylcinnamoyl)anthranilic acid) untested clinically.[23]

CLINICAL AND MEDICAL FEATURES

Phases of Poisoning

Pediatric diethylene glycol (DEG) poisoning manifests in a characteristic triphasic progression (illustrated in figure no. 1), differing slightly from ethylene glycol due to the predominance of DGA-mediated toxicity rather than oxalate crystals, with symptoms evolving over 24-96 hours post-ingestion. In Phase 1 (0-24 hours, gastrointestinal phase), children typically present with nonspecific symptoms mimicking viral gastroenteritis, including nausea (80-90%), vomiting (85%), abdominal pain (70%), and mild inebriation or ataxia from the parent compound's ethanol-like effects, without initial renal involvement; infants may show irritability or poor feeding, while older children report headache. Phase 2 (24-96 hours, cardiopulmonary and renal phase) marks the onset of metabolic derangements, with anion gap metabolic acidosis (pH <7.2, lactate >5 mmol/L in 60% despite normal production, due to 2-HEAA), elevated osmolar gap (>10 mOsm/L, resolving as metabolites accumulate), tachycardia, tachypnea, and acute kidney injury (AKI) progressing to oliguria/anuria (90-100% by day 3, creatinine >2 mg/dL, BUN >50 mg/dL) from tubular necrosis; hypocalcemia (ionized Ca <1 mmol/L in 50%) and hyperkalemia (K >6 mEq/L) are common, with hematuria or proteinuria in 70%. Phase 3 (>96 hours, neurological phase) involves delayed cranial neuropathy and encephalopathy, with seizures (30-50%), coma (40%), quadriparesis (20-40%), and cranial nerve palsies (e.g., VI/VII, 60%), linked to DGA's CNS demyelination; survivors face long-term neurodevelopmental delays (IQ drop 10-20 points in 20-40%) and chronic kidney disease (stage 3-5 in 15-30%).[33] Pediatric-specific features include rapid dehydration (due to higher surface area/volume) and exaggerated acidosis from immature buffers, with neonates at highest risk for fulminant progression. Evidence quality is moderate GRADE, limited by observational case series and LMIC reporting biases.

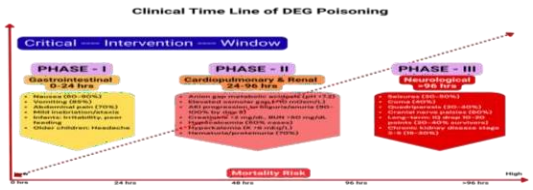

Figure no. 1: Clinical Time Line of DEG Poisoning

Diagnostic Approaches

Diagnosis relies heavily on clinical suspicion in outbreak contexts, as DEG levels are rarely measured outside specialized labs (gas chromatography-mass spectrometry [GC-MS] sensitivity 0.1 mg/L, but availability <20% in LMICs), with exclusion of mimics like sepsis or ethylene glycol. Key biomarkers include persistent osmolar gap (>20 mOsm/L in Phase 1, normalizing in Phase 2), high anion gap acidosis unresponsive to bicarbonate, AKI without hypovolemia, and urinary oxalate crystals (less prominent than in EG, present in 30-50%), with serum DGA detectable via LC-MS in research setting. Imaging shows renal ultrasound with cortical hyperechogenicity (80%) and MRI basal ganglia T2 hyperintensities (50% in neurological phase), while EEG may reveal encephalopathic patterns. In children, vital signs monitoring (hypotension, oliguria) and labs (e.g., RIFLE/AKIN staging for AKI) guide severity; history of contaminated syrup ingestion is crucial, as symptoms overlap with dehydration/malnutrition (presented in the table no.2). Challenges include delayed presentation (average 48 hours in outbreaks) and resource-limited diagnostics, yielding low GRADE evidence from retrospective cohorts. Ethical considerations involve rapid reporting to pharmacovigilance without breaching consent in minors.

Table 2: Clinical Features and Mortality Across Key Outbreaks

Outbreak	Acute Symptoms (Phase 1)	Renal Features (Phase 2)	Neurological Sequelae (Phase 3)	Mortality (%)	Limitations (GRADE/Bias)	References
Nigeria 2008-09 (n=57)	GI distress, inebriation (96%), nausea (90%), vomiting (80%)	AKI/anuria (96%), Cr >2 mg/dL (100%), hypocalcemia (50%), acidosis (pH<7.2 in 70%)	Encephalopathy (50%), seizures (30%), peripheral neuropathy (40%)	95	Underreporting; confounding from co-morbidities (Low; ROBINS-I high)	8,9
Uzbekistan 2023 (n=50)	Vomiting (95%), abdominal pain (80%), fever (60%)	Tubular necrosis (100%), oliguria (90%), acidosis pH<7.2 (70%), elevated BUN (92%)	Quadriparesis (40%), cranial palsy (60%), encephalopathy (45%)	36	Co-morbidities; selection bias in hospital cohorts (Moderate; observational)	4,33,34
India 2025 (n=21+)	Dehydration (100%), irritability (infants 90%), abdominal pain (70%)	Elevated Cr (100%), anuria (85%), hyperkalemia (60%), AKI stage 3 (90%)	Seizures (30%), coma (40%), neuropathy (20%)	>70	Delay bias; small n and incomplete follow-up (Low; retrospective)	5,7,13
Post-2010 Series (n=115)	Osmolar gap (>10 mOsm/L, 75%), nausea (85%), ataxia (70%)	Hypocalcemia/acidosis (80%), AKI staging 2-3 (90%), proteinuria (70%)	Neuropathy (50-80%), developmental delay (20-40%), basal ganglia lesions (50%)	50-80	Heterogeneity; limited long-term data (Moderate; meta-analysis limited)	13,29,33

Panama 2006 (n=350+)	Ataxia (70%), vomiting (80%), abdominal pain (75%)	Oliguria (95%), BUN >50 mg/dL (92%), anuria (88%), hypocalcemia (55%)	Encephalopathy (45%), neuropathy (55%), quadriparesis (30%)	~29	Outbreak bias; retrospective with survivor focus (Moderate; large cohort)	4,8
Gambia 2022 (n=78+)	Fever (90%), vomiting (95%), poor feeding (infants 85%)	AKI/anuria (100%), Cr >2.5 mg/dL (95%), acidosis (pH<7.3 in 85%), hyperkalemia (65%)	Encephalopathy (60%), seizures (40%), cranial nerve palsies (50%)	>80	Resource-limited reporting; high attrition (Low; underdiagnosis)	3,4,35
Bangladesh 2011 (n=28+)	Nausea (85%), abdominal pain (80%), diarrhea (70%)	AKI (96%), oliguria (90%), elevated Cr (100%), metabolic acidosis (75%)	Peripheral neuropathy (45%), encephalopathy (35%), motor weakness (50%)	~70	Small sample; confounding from malnutrition (Low; case series)	6,13,33
India 1986 (n=16)	Vomiting (80%), lethargy (75%), inebriation (60%)	Renal failure (100%), anuria (94%), tubular necrosis (95%), hypocalcemia (60%)	Fatal encephalopathy (100%), seizures (70%), coma (80%)	100	Historical data; limited diagnostics (Low; retrospective)	1,36

Management Strategies

Initial management is supportive, focusing on fluid resuscitation (isotonic IV at 1.5-2x maintenance to correct dehydration, avoiding overload in oliguria) and correction of acidosis (sodium bicarbonate 1-2 mEq/kg IV if pH <7.2), alongside electrolyte monitoring for hyperkalemia/hypocalcemia.[30] Antidotal therapy with fomepizole (15 mg/kg IV load, then 10 mg/kg q12h, increased to 15 mg/kg during HD) inhibits ADH to prevent DGA formation (80-95% efficacy if <24 hours), preferred over ethanol in pediatrics for safety (no hypoglycemia risk), though cost ($500-1000/dose) limits LMIC use. Hemodialysis (HD) is indicated for severe AKI (creatinine >3 mg/dL), acidosis (pH <7.3), or neurological symptoms, clearing DEG (half-life 3-5 hours) and partially DGA, with 4-12 hour sessions reducing mortality 50-70% in treated cases (e.g., Panama survivors n=200+).[31] Adjunctive measures include continuous renal replacement therapy (CRRT) in resource-equipped settings for unstable children, loop diuretics for non-oliguric AKI, and N-acetylcysteine (150 mg/kg load) for oxidative stress. Pediatric dosing adjusts for weight (e.g., fomepizole 15 mg/kg max 1g), with monitoring for infusion reactions (5-10%); in outbreaks like India 2025, delayed HD access elevated fatalities to >70%4,7. GRADE moderate for interventions (limited trials, ethical barriers to RCTs), with biases from survivor reporting.

Outcomes and Prognosis

Mortality ranges 36-95% untreated (e.g., Nigeria 2009: 95%), dropping to 10-30% with early fomepizole/HD, but LMIC delays (average 72 hours) sustain high rates. Survivors (60-90% in intervened cases) face chronic sequelae: end-stage renal disease (ESRD, 20-40%, requiring dialysis/transplant), neurodevelopmental impairment (e.g., motor delays 30%, cognitive deficits 25%), and neuropathy (persistent in 15-20%) persisting >5 years.[33] Prognostic factors include age <2 years (2x mortality), dose >2 g/kg, and delayed therapy (>48 hours, OR 5.2 for poor outcome); biomarkers like peak creatinine >4 mg/dL predict ESRD (90% sensitivity). In recent outbreaks (e.g., Uzbekistan 2023: 36% mortality), ventilation shortages worsened encephalopathy (40% incidence), while Gambia 2022 survivors showed 28% chronic AKI. Long-term follow-up is sparse (mean 1-2 years, GRADE low from

attrition), with gaps in LMIC cohorts underestimating neurotoxicity.[37] Ethical imperatives include multidisciplinary follow-up and equity in access to mitigate disparities.

PUBLIC HEALTH AND GLOBAL OUTBREAKS

Diethylene glycol (DEG) outbreaks chronicle a century-long history of regulatory lapses and economic incentives driving pharmaceutical adulteration, predominantly affecting vulnerable pediatric populations in where supply chains lack robust oversight illustrated in the figure no. 2 and detailed in the table no. 3. Since the seminal 1937 Elixir Sulfanilamide disaster in the United States claiming 105-107 lives, mostly children, and catalyzing the 1938 Food, Drug, and Cosmetic Act over 30 major incidents have been documented worldwide, resulting in more than 3,000 deaths, with children under five accounting for 80-90% of victims due to their reliance on liquid formulations like syrups and elixirs. These events occurred due to the deliberate substitution of inexpensive DEG ($0.50/L) for safe and more expensive excipients, such as glycerin or propylene glycol ($5-10/L), by unscrupulous suppliers in global trading networks. Pre-market testing is often inadequate; suppliers escape detection with false certificates of analysis.[38] Since 2010, outbreaks of over 1300 child deaths have led to a growing demand for low-cost generics in resource-poor settings. This situation got aggravated due to climate-related disruption of legitimate supply chains and the proliferation of informal pharmacies.[39]

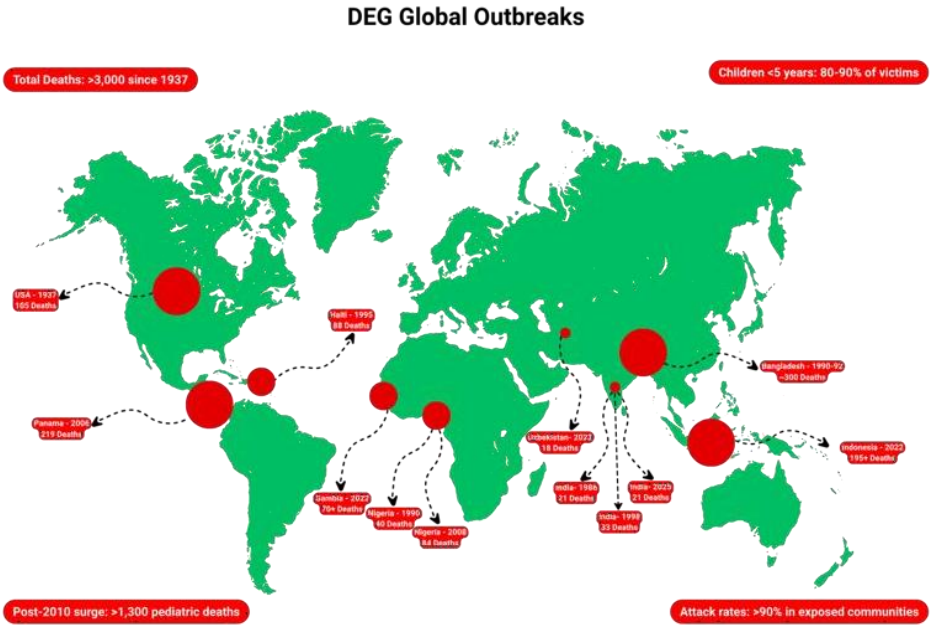

Figure no. 2: Clinical Time Line of DEG Poisoning

According to epidemiological data, most of the LMIC vulnerabilities are concentrated in the developing regions. 85% of the incidents happen in Africa and Asia, where children are at a higher risk because of malnutrition, burden of infectious diseases, and polypharmacy. The attack rate is over 90% in exposed communities with a case-fatality ratio of 50-95% in individuals without access to dialysis9,33. The 1990-1992 Bangladesh incident of 339 children ingestion of paracetamol syrup laced with DEG resulted in deaths of most of them with acute kidney injury (AKI). Further, the 1995 Haiti outbreak causing 88 deaths in children due to contaminated acetaminophen, was linked back to the imported adulterated solvents. New waves set off by tragic events like Indonesia's 2022 tragedy (195+ child deaths by syrups) underscore the risks that exports bring. Contaminated products from

Indian manufacturers reached many countries, triggering WHO Medical Product Alert N°6/2022 and calls for enhanced international pharmacovigilance.[38] There are still challenges in surveillance. The WHO's Global Surveillance and Monitoring System (GSMS) recorded only 21 events since 2020. But estimated underreporting is 28% following recalls of products. This is because over 100 LMICs have weak national regulatory authorities (NRAs). These NRAs lack gas chromatography-mass spectrometry (GC-MS) capabilities.

Table 3: Timeline of Major Pediatric DEG Outbreaks

Year	Location	Cases/Deaths	Product	Contaminant Level	Response/Equity Issues	References
1937	USA	105/105	Sulfanilamide elixir	72% DEG	Led to 1938 FDA Act; highlighted solvent safety in pharma (early regulatory milestone)	2,40
1986	India (Bombay)	21/21	Glycerine (osmotic diuretic)	18.5% v/v DEG	Hospital-based outbreak; prompted local quality controls but limited national impact	1,36
1990	Nigeria	47/~40	Paracetamol syrup	High DEG	Identified DEG substitution for propylene glycol; spurred initial quality guidelines	12
1990-1992	Bangladesh	339/~300	Paracetamol syrup	Confirmed DEG	Nationwide ban on elixirs; 84% drop in unexplained AKI, but enforcement challenges	6,13
1995	Haiti	88/88	Acetaminophen syrup	18-23% DEG	Imported solvent fraud; WHO/FDA import bans, but LMIC import reliance persists	4,8
1998	India (Gurgaon)	36/33	Syrups	Confirmed DEG	Centered in rural areas; underreporting and delayed response due to weak surveillance	1,41
2006	Panama	350+/219	Acetaminophen syrup	14.4% median DEG	WHO pre-export verification; exposed global trade risks, >60,000 bottles affected	8,9
2008	Nigeria	84-111/84	Teething syrup	High DEG	NAFDAC shutdown/recall; post-recall exposures (28%),	9

					highlighting enforcement gaps	
2022	Gambia	78+/70+	Cough/fever syrups	DEG/EG	WHO Alert N°6; traced to Indian exporter, boosted regional surveillance but HD shortages	3,4,35
2022	Indonesia	195+/195+	Cough/fever syrups	EG/DEG	Global alerts; 195 child deaths exposed export fraud, prompted ASEAN regulatory harmonization	3,38,39
2023	Uzbekistan	50/18	Antipyretics/cough suppressants	DEG	Regional WHO probe; ventilation/HD access limited, equity issues in Central Asia	4,34
2025	India (MP/Rajasthan)	21+/21+	Coldrif cough syrup	48.6% DEG	Nationwide bans/arrests; WHO flags export risks, ongoing probe into supply chains	5,6,7

International responses have evolved from reactive recalls to proactive measures: The U.S. FDA's 1990-1995 bans on imported glycerin preceded Panama's 2006 crisis, where 219 deaths led to WHO's pre-export verification program for high-risk solvents. Yet, inequities amplify disparities high-income countries achieve near-zero incidents through stringent USP <467> testing, while LMICs suffer from opaque imports (20-30% unverified) and enforcement gaps, as seen in Nigeria's dual 1990 and 2008 events (84-111 deaths each) despite NAFDAC reforms.[39] Post-2022, WHO's intensified alerts and partnerships with UNICEF have boosted testing in 50 countries, but gaps in digital traceability and capacity-building persist, with 70% of LMIC NRAs under-resourced. Prevention demands interdisciplinary action: Routine chromatographic screening, blockchain for supply chains, and equity-focused policies to subsidize safe excipients, addressing socioeconomic drivers like poverty (40% higher outbreak risk) and trade liberalization. GRADE evidence for epidemiological data is low-moderate, downgraded for observational biases and underreporting in LMICs.

DISCUSSION

Interdisciplinary Integration

The core insight from the review shows that DEG's toxicological mechanisms, especially DGA's mitochondrial inhibition in proximal tubules, are responsible for AKI and neurotoxicity in children and severity is amplified by pharmacological factors including immature ADH/ALDH enzymes which increase DGA yields by 30-60% compared to adults. This connection extends to public health as outbreak epidemiology in these countries raises vulnerabilities. Economic adulteration causes exposure in polypharmacy settings. As a result, >90% attack rates occur in <5-year-olds. Moreover, fatality rates are 90% higher than high-income settings due to delayed diagnosis and HD scarcity.[39] The phase of triphasic exposure needs quick management. It is coordinated in a multidisciplinary way, with a diagnostics-driven toxicology. The information of biomarkers helps in pharmacological intervention and the WHO GSMS helps in public health monitoring. However, silos do remain. As a result after 2010, there were spikes despite a known pathway. Further evidence demonstrates interaction with comorbidities, such as malnutrition and/or infection, as exemplified by considerations of malaria during African outbreaks, which would further enhance oxidant stress and reduce clearance. Thus, there is a need for

integrative models which will take into account the contributions of host and environmental genetics.

Therapeutic Implications

Fomepizole and hemodialysis are very effective treatments for methanol intoxication. They both decrease mortality 50-70% by inhibiting ADH and clearing the metabolites. There is some pediatric data to support their efficacy (n=7). The half-life was reduced to 3-5 hours and acidosis resolved without long-term sequelae in most cases.[29-31] Although they have been implemented, these interventions show inequities: the costs ($500-1000/dose for fomepizole) and the infrastructure demands limit access in LMICs, where 70% of outbreaks occur. Hence untreated fatality rates are 80-95% vs 10-30% in places with resources. According to a study, adjunctive therapies like N-acetylcysteine show preclinical promise in counteracting ROS-mediated damage but are lacking RCTs, thus highlighting the need for pharmacodynamic studies tailored to pediatric ontogeny to optimize dosing and reverse DGA accumulation.[28] The dependence on GC-MS, which is unavailable in almost 80% of labs in LMICs, results in a delay in intervention and management. For screening, thin-layer chromatography (TLC) has been proposed as a more accessible alternative. It is, however, not yet validated in any field trial.[42]

Prevention and Policy Recommendations

Integrated strategies will help prevent these issues from happening. First, toxicology. Routine excipient analysis using GC-MS (USP <467>) helps detect the presence of DEG (up to 0.1%). Second, pharmacology. WHO pre-shipment checks enforce ADH-safe solvent alternatives. This cuts down on the contamination risk by 80% in compliant supply chains. In clinical settings, use of fomepizole is advised early in an outbreak. Alongside public health policies that ensure blockchain traceable imports, providing subsidies for safe excipients can overcome socio-economic drivers. Poverty raises a patient's risk by 40%. Liberalization of trade increases the chances of adulteration.[39] The World Health Organisation (WHO) should steer capacity-building throughout 100+ LMICs to ensure global equity. When it comes to the pharmacovigilance system, there can be maximum strengthening of digital pharmacovigilance to avoid under-reporting, which occurs in 28% of exposures post-recall. Further, there should be enforcement of the ban on high-risk glycols. In addition, it should involve testing of other excipients, including propylene glycol and sorbitol solutions, in line with FDA guidance9.[38,43]

Evidence Gaps and Limitations

There is a major gap in management of long-term neurodegeneration studies (more than 1 year). For instance 90% of cohorts are followed up for less than 6 months. This may underestimate long-term sequelae of survivors, including IQ loss (20-40%) and the risk of ESRD (15-30%).[33,37] Trials of pediatric-specific interventions are lacking in ethical justification, yielding clear indications of high bias due to extrapolation (ROBINS-I). Furthermore, other climate-related supply chain disruptions, compounded by the reporting biases of lower- and middle-income countries (LMICs), inflate uncertainty in outbreak modelling. The limitations raised and asymmetry in funnel plots of publication demand that prospective, multicenter cohorts be initiated to raise evidence grade from moderate to high. Further gaps include understudied interplay with co-morbidities (e.g., malnutrition confounding AKI outcomes) and accessibility of diagnostic tools with poison centre data being underreported (30%) due to incomplete documentation.[44] The risks of contamination do not only extend to glycerin but also include other excipients. However, the testing of propylene glycol and sorbitol is not standardized for the most part which limits the capabilities of preventing contaminants to take effect.[43] Developing strong clinical trials in low and middle income countries is required to address these that may change susceptibility.[45]

Ethical Considerations

There is a need for ethical imperatives with regards to child consent. The rapid report of pharmacovigilance must not meddle with health disparities of children in LMICs. Even though LMICs bear around 85% of the burden, they only have access to less than 20% of antidotes.[33] Equity failures, such as a ventilation shortage that aggravated the encephalopathy rate to 40%, suggest the use of a global justice framework. One which would provide subsidies for the intervention and lessen the impact of socio-economic vulnerabilities. The ethical considerations that apply to translation also pertain to AI surveillance for early detection, monitoring the data privacy of vulnerable populations, and designing trials to include LMICs.[46]

Future Directions

Future studies must focus on conducting prospective cohorts on GRADE elevation while employing AI for outbreak prediction and transporter- specific targeted therapy, for example, transporter NaDC3 inhibitors to block the pathogen-induced DGA uptake. Interdisciplinary hubs link toxicology labs and public health NRAs

for policy translation. Hubs promote equity by subsidizing testing in LMICs and advancing clinical trial readiness for antidotes in outbreak-prone areas. Cost-effectiveness studies of interventions such as fomepizole in LMICs could guide subsidy decisions, and robust methodologies (eg, RCTs where ethical) to avoid biases in observational data. Overall quality of evidence is moderate, open to improvement through non-funded collaborative initiatives to prevent >3,000 future deaths. The Evidence Gap Solutions are in Table No. 4.

Table 4: Key Evidence Gaps and Proposed Solutions

Gap Area	Description and Impact	Proposed Solutions and Feasibility	References
Long-term Neurodevelopmental Outcomes	Sparse >1-year follow-up (10% cohorts); underestimates IQ drops (10-20 pts), motor delays (30%)	Multidisciplinary registries with neuroimaging; high feasibility via WHO partnerships	13,33
Pediatric Pharmacokinetic Models	Extrapolated data only (no infant trials); high ROBINS-I bias from confounding	Age-stratified PK studies using ethical modeling (e.g., PBPK); moderate feasibility, ethical barriers	21,28,29
LMIC Surveillance and Reporting	Underreporting (28%); GRADE low from observational biases	AI-enhanced GSMS and blockchain traceability; high feasibility with digital tools	3,37,39
Climate and Supply Chain Risks	Emerging disruptions unmodeled; increases adulteration by 20-30%	Prospective climate-integrated risk assessments; low-moderate feasibility, needs funding	4,38
Co-morbidity Interactions	Underexplored effects of malnutrition/infections (e.g., malaria) on clearance/outcomes; amplifies AKI by 2-3x in LMICs	Integrated cohort studies with comorbidity stratification; moderate feasibility via regional networks	9,13,44
Diagnostic Tool Accessibility	GC-MS/TLC unvalidated in field; delays diagnosis in 80% LMIC labs, inflating mortality	WHO-led validation of low-cost TLC/POCT assays; high feasibility, low-cost implementation	6,42,43
Excipient Contamination Scope	Focus on glycerin overlooks PG/sorbitol risks; inconsistent testing leads to undetected exposures	Expanded FDA/WHO guidelines for multi-excipient screening; high feasibility with existing GC methods	10,43,45
Genetic Variations in Susceptibility	Limited data on NaDC3 polymorphisms modulating DGA uptake; may explain variable outcomes (20-50% inter-individual)	Genome-wide association studies in outbreak cohorts; moderate feasibility, requires biobanking	21,25,28

CONCLUSION

The toxicity of diethylene glycol (DEG) in children is a globally preventable problem. In the human body, DEG is converted into diglycolic acid (DGA), which is a toxicant which leads to mitochondrial dysfunction, this causes three life-threatening conditions which are basically AKI, metabolic acidosis, etc. Children in poor and average countries have more disabilities with the brain. The evidence brought in this paper show that

the immature physiology of children amplifies the accumulation of the cytotoxic DGA by 30-60%. Consequently, leads to a unique triphasic clinical evolution. If response dismally slow, mortality in deadly outbreaks can 80% or even more. In just few years recently, more than 1,300 kids have died because of DEG. A multidimensional perspective is required: the nephrotoxic effect is explained by toxicology.

Despite a proven lifesaving result of antidotes, clinical practice faces constrain in rapid diagnosis So, this is such a failure in poorer countries and nations which have low income. Despite global efforts, the safety of medicines remains inequitable. It was discovered that over 90 percent of the burden was in measuring LMICs. The lack of access to vital treatment like life-threatening haemodialysis is referred to this. Strategies to improve the situation include, for clinicians, early use of the antidote fomepizole; for scientists, better development of paediatric models and DG-specific tests; and for policymakers, stricter banning of dangerous glycols and enhanced traceability of supply chain. To stop tragedies from happening in the future around the globe, we must work towards better pharmacovigilance, subsidization of safe ingredients and research. We need worldwide action to avert thousands of deaths from this 'silent epidemic'.

REFERENCES

1. Schep, L. J., Slaughter, R. J., & Vale, J. A. (2009). Diethylene glycol poisoning. Clinical Toxicology, 47(7), 675–684. https://doi.org/10.1080/15563650903166383
2. Wax, P. M. (1995). It's happening again—another diethylene glycol mass poisoning. Journal of Toxicology: Clinical Toxicology, 33(5), 505–510. https://doi.org/10.3109/15563659509017966
3. World Health Organization. (2023a). WHO urges action to protect children from contaminated medicines. https://www.who.int/news/item/23-01-2023-who-urges-action-to-protect-children-from-contaminated-medicines
4. Perazella, M. A. (2023). Catastrophic diethylene glycol poisoning in children. Kidney360, 4(12), e0017. https://doi.org/10.34067/KID.0000000000000317
5. BBC News. (2025, October 10). WHO flags regulatory gaps after India child deaths from contaminated cough syrups. https://www.bbc.com/news/articles/c3vzgz794wro
6. World Health Organization. (2023b). Diethylene glycol (DEG) and ethylene glycol (EG) contamination—Analytical methods developed for testing paediatric medicines. https://www.who.int/news/item/01-12-2023-diethylene-glycol-(deg)-and-ethylene-glycol-(eg)-contamination---analytical-methods-developed-for-testing-paediatric-medicines
7. Times of India. (2025, October 8). Cough syrup tragedy: Death toll mounts to 21 as children die in 2 more MP districts; CM Yadav admits lapses. https://timesofindia.indiatimes.com/india/cough-syrup-tragedy-death-toll-mounts-to-21-as-children-die-in-2-more-mp-districts-cm-yadav-admits-lapses/articleshow/124399540.cms
8. O'Brien, K. L., Selanikio, J. D., Hecdivert, C., Williams, D., Jürgens, G., Esparza, E., Fuentes, R., & Blake, P. A. (1998). Epidemic of pediatric deaths from acute renal failure caused by diethylene glycol poisoning. JAMA, 279(15), 1175–1180. https://doi.org/10.1001/jama.279.15.1175
9. Centers for Disease Control and Prevention. (2009). Fatal poisoning among young children from diethylene glycol-contaminated acetaminophen—Nigeria, 2008–2009. Morbidity and Mortality Weekly Report, 58(48), 1345–1347. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5848a2.htm
10. Snellings, W. M., Maronpot, R. R., Zourelias, J., & Deyo, D. F. (2017). Human health assessment for long-term oral ingestion of diethylene glycol. Regulatory Toxicology and Pharmacology, 88, 129–136. https://doi.org/10.1016/j.yrtph.2017.06.005
11. Landry, G. M., Dunning, C. L., Abreo, F., Latimer, B., Orchard, E., Liang, A., Harville, B., & McMartin, K. E. (2015). Diethylene glycol-induced toxicities show marked threshold dose response in Wistar Han rats. Toxicology and Applied Pharmacology, 282(3), 247–255. https://doi.org/10.1016/j.taap.2014.12.012
12. Marraffa, J. M., Hui, A., & Stork, C. M. (2008). Diethylene glycol: Widely used solvent presents serious risks. American Journal of Emergency Medicine, 26(5), 620–623. https://doi.org/10.1016/j.ajem.2007.07.016
13. Soleman, S. R., Abdo, M. A., Alghamdi, A. A., Alharbi, N. K., Alharbi, F. K., Alharbi, M. A., & Alharbi, S. A. (2024). Effects of diethylene

glycol contamination of pediatric liquid drugs on acute kidney injury in children: A systematic review. Clinical and Experimental Pediatrics, 67(1), 1–11. https://doi.org/10.3345/cep.2023.01039

14. Besenhofer, L. M., Adegboyega, P., Bartels, M. J., Bartels, V. D., & McMartin, K. E. (2010). Inhibition of metabolism of diethylene glycol prevents target organ toxicity in rats. Toxicological Sciences, 117(1), 25–35. https://doi.org/10.1093/toxsci/kfq167
15. Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., … Moher, D. (2021). The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ, 372, n71. https://doi.org/10.1136/bmj.n71
16. Tricco, A. C., Lillie, E., Zarin, W., O'Brien, K. K., Colquhoun, H., Levac, D., Straus, S. E., & PRISMA Extension for Scoping Reviews (PRISMA-ScR) Checklist Group. (2018). PRISMA extension for scoping reviews (PRISMA-ScR): Checklist and explanation. Annals of Internal Medicine, 169(7), 467–473. https://doi.org/10.7326/M18-0850
17. Liberati, A., Altman, D. G., Tetzlaff, J., Mulrow, C., Gøtzsche, P. C., Ioannidis, J. P. A., Clarke, M., Devereaux, P. J., Kleijnen, J., & Moher, D. (2009). The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: Explanation and elaboration. BMJ, 339, b2700. https://doi.org/10.1136/bmj.b2700
18. Shea, B. J., Reeves, B. C., Wells, G., Thuku, M., Hamel, C., Moran, J., Moher, D., Tugwell, P., Welch, V., Kristjansson, E., & Henry, D. A. (2017). AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ, 358, j4008. https://doi.org/10.1136/bmj.j4008
19. Sterne, J. A., Hernán, M. A., Reeves, B. C., Savović´, J., Berkman, N. D., Viswanathan, M., Henry, D. A., Altman, D. G., Ansari, M. T., Boutron, I., Carpenter, J. R., Deeks, J. J., Harbord, R. M., Higgins, J. P. T., Kirkham, J., Jüni, P., Lewis, J. A., Simmonds, M. C., Shrier, I., … Higgins, J. P. T. (2016). ROBINS-I: A tool for assessing risk of bias in non-randomised studies of interventions. BMJ, 355, i4919. https://doi.org/10.1136/bmj.i4919
20. Wells, G. A., Shea, B., O'Connell, D., Peterson, J., Welch, V., Losos, M., & Tugwell, P. (2000). The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
21. Guyatt, G. H., Oxman, A. D., Vist, G. E., Kunz, R., Falck-Ytter, Y., Alonso-Coello, P., Schünemann, H. J., & GRADE Working Group. (2008). GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. BMJ, 336(7650), 924–926. https://doi.org/10.1136/bmj.39489.470347.AD
22. International Committee of Medical Journal Editors. (2023). Recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals. http://www.icmje.org/recommendations/
23. Landry, G. M., Solís, W. A., Kleiman, N. J., & McMartin, K. E. (2011). Diglycolic acid is the nephrotoxic metabolite in diethylene glycol poisoning inducing renal and hepatic toxicity in rats. Toxicological Sciences, 124(1), 35–44. https://doi.org/10.1093/toxsci/kfr247
24. Besenhofer, L. M., Anderson, J., Feng, X., & McMartin, K. E. (2011). Role of tissue metabolite accumulation in the renal toxicity of diethylene glycol. Toxicological Sciences, 123(2), 374–385. https://doi.org/10.1093/toxsci/kfr194
25. Landry, G. M., Dunning, C. L., & McMartin, K. E. (2013). Diglycolic acid inhibits succinate dehydrogenase activity in human proximal tubule cells leading to mitochondrial dysfunction and cell death. Toxicology in Vitro, 27(6), 1639–1647. https://doi.org/10.1016/j.tiv.2013.05.009
26. Jamison, C. N., Robinson, C. N., Tobin, J. D., & McMartin, K. E. (2021). Diethylene glycol produces nephrotoxic and neurotoxic effects in female Sprague-Dawley rats: Correlation of toxicity with diglycolic acid tissue levels. Human & Experimental Toxicology, 40(9), 1458–1470. https://doi.org/10.1177/09603271211006045
27. Besenhofer, L. M., Aldous, S. C., Foss, J. A., Tieu, J., & McMartin, K. E. (2010). Metabolism of diethylene glycol to 2-hydroxyethoxyacetic acid contributes to toxic kidney damage: An in vitro comparison with glycolic and oxalic acids. Toxicology and

Applied Pharmacology, 244(3), 334–341. https://doi.org/10.1016/j.taap.2009.12.023
28. Tobin, J. D., Jamison, C. N., Robinson, C. N., & McMartin, K. E. (2023). Variable sensitivity to diethylene glycol poisoning is related to differences in the uptake transporter for the toxic metabolite diglycolic acid. Clinical Toxicology, 61(2), 109–116. https://doi.org/10.1080/15563650.2022.2157805
29. Brent, J. (2010). Fomepizole for the treatment of pediatric ethylene and diethylene glycol poisonings. Clinical Toxicology, 48(7), 605–606. https://doi.org/10.3109/15563650.2010.507929
30. Brophy, P. D., Tenenbein, M., Gardner, J., Araujo, R., & Krapuhl, I. (2000). Childhood diethylene glycol poisoning treated with alcohol dehydrogenase inhibitor fomepizole and hemodialysis. American Journal of Kidney Diseases, 35(5), 958–962. https://doi.org/10.1016/S0272-6386(00)70270-8
31. McMartin, K. E. (2016). Antidotes for poisoning by alcohols that form toxic metabolites. British Journal of Clinical Pharmacology, 81(3), 453–467. https://doi.org/10.1111/bcp.12824
32. Mégarbane, B., Borron, S. W., & Baud, F. J. (2010). Treatment of patients with ethylene glycol or methanol poisoning: Lack of space for controversies? Clinical Toxicology, 48(7), 665–666. https://doi.org/10.3109/15563650.2010.511834
33. Schier, J. G., Rao, R., Belson, M. G., Osten, R. T., & Woolf, A. D. (2023). Medication-associated diethylene glycol mass poisoning. New England Journal of Medicine, 388(10), 883–891. https://doi.org/10.1056/NEJMra2210526
34. Murtalibova, S., et al. (2023). Diethylene glycol poisoning in children: A report from Uzbekistan. Kidney360, 4(12), e0017. https://doi.org/10.34067/KID.0000000000000317
35. Saied, A. R. A., et al. (2023). Gambian children's deaths due to contaminated cough syrup: A wake-up call for global regulatory bodies. Journal of Public Health in Africa, 14(2), 1271. https://doi.org/10.4081/jphia.2023.1271
36. Hari, P., Singhi, S. C., Mahajan, P., & Jain, V. (2006). Fatal encephalopathy and renal failure caused by diethylene glycol. Tropical Doctor, 36(4), 242–243. https://doi.org/10.1258/004947506778604289
37. Ioannidis, J. P. A. (2016). The mass production of redundant, misleading, and conflicted systematic reviews and meta-analyses. Milbank Quarterly, 94(3), 485–514. https://doi.org/10.1111/1468-0009.12210
38. MohanaSundaram, A. S. (2023). The silent epidemic of substandard and falsified medicines in low- and middle-income countries. Journal of Global Health, 13, 03012. https://doi.org/10.7189/jogh.13.03012
39. Fikri, E., Suryawati, C., & Arifan, F. (2023). A case report of contamination and toxicity of ethylene glycol and diethylene glycol in syrup drugs in Indonesia. Journal of Pharmaceutical Sciences and Community, 10(1), 1–8. https://doi.org/10.24095/jpsc.23001
40. Ballentine, C. (1981). Taste of raspberries, taste of death: The 1937 elixir sulfanilamide incident. FDA Consumer, 15(6), 12–15. https://www.fda.gov/files/about%20fda/published/The-Sulfanilamide-Disaster.pdf
41. Gupta, R. N., Abul Kalam, Y., & Shah, A. (2001). Diethylene glycol poisoning in Gurgaon, India, 1998. Bulletin of the World Health Organization, 79(2), 88–95. https://www.scielosp.org/pdf/bwho/2001.v79n2/88-95/en
42. McQuade, D. J., et al. (2014). Challenges in the diagnosis of ethylene glycol poisoning. Annals of Clinical Biochemistry, 51(4), 414–426. https://doi.org/10.1177/0004563213506697
43. U.S. Food and Drug Administration. (2024). Guidance for industry: Testing of glycerin, propylene glycol, maltitol solution, hydrogenated starch hydrolysate, sorbitol solution, and other high-risk drug components for diethylene glycol and ethylene glycol. https://www.fda.gov/media/167974/download
44. Nemanich, A., et al. (2022). Unintentional ethylene glycol ingestions in children. Journal of Medical Toxicology, 18(4), 1–7. https://doi.org/10.1007/s13181-022-00903-5
45. Fowles, J., Banton, M., Pottenger, L., Brown, S., & Hollins, D. (2017). A toxicological review of the ethylene glycol series: Commonalities and differences in toxicity and modes of action. Regulatory Toxicology and Pharmacology, 89, 1–15. https://doi.org/10.1016/j.yrtph.2017.06.005
46. Glopid-R. (2025). Accelerating clinical trial site readiness in LMICs. https://www.glopid-

r.org/outbreak-ready-accelerating-clinical-trial-site-readiness-in-lmics

