DEG/EG Contamination of Medical Products: Current Situation

Joint UNICEF, UNFPA and WHO manufacturers and suppliers meeting

Copenhagen, Denmark

30 November 2023

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Team Lead, Incidents and Substandard/Falsified medical products team

World Health Organization

Historical incidents of DEG/EG contamination

1937

USA

DEG-contaminated Elixir Sulfanilamide. >100 deaths. Led to enactment of the Federal Food, Drug, and Cosmetic Act

1990-1998

Argentina, Bangladesh, India, and Nigeria

DEG poisoning reportedly occurred, hundreds of deaths.

1996

Haiti

> 68 cases of AKI in children. > 30 deaths. DEG contaminated Paracetamol syrups. Local Products.

2006

Panama

> 82 cases of AKI. > 38 deaths. Syrup preparations & topical creams contaminated with DEG

2008-2009

Nigeria

>84 children died. DEG contaminated Paracetamol syrup. Local products

2019

India

>17 suspect AKI cases in children. >12 deaths reported. DEG contaminated Paracetamol syrup

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Press coverage then…

The New York Times

F.D.A. Tracked Poisoned Drugs, but Trail Went Cold in China

Give this article

By Walt Bogdanich
June 17, 2007

After a drug ingredient from China killed dozens of Haitian children a decade ago, a senior American health official sent a cable to her investigators: find out who made the poisonous ingredient and why a state-owned company in China exported it as safe, pharmaceutical-grade glycerin.

The Chinese were of little help. Requests to find the manufacturer were ignored. Business records were withheld or destroyed.

The Americans had reason for alarm. "The U.S. imports a lot of Chinese glycerin and it is used in ingested products such as toothpaste," Mary K. Pendergast, then deputy commissioner for the Food and Drug Administration, wrote on Oct. 27, 1997. Learning how diethylene glycol, a syrupy poison used in some antifreeze, ended up in Haitian fever medicine might "prevent this tragedy from happening again," she wrote.

The F.D.A.'s mission ultimately failed. By the time an F.D.A. agent visited the suspected manufacturer, the plant was shut down and Chinese companies said they bore no responsibility for the mass poisoning.

Ten years later it happened again, this time in Panama. Chinese-made diethylene glycol, masquerading as its more expensive chemical cousin glycerin, was mixed into medicine, killing at least 100 people there last year. And recently, Chinese toothpaste containing diethylene glycol was found in the United States and seven other countries, prompting tens of thousands of tubes to be recalled.

Five jailed in Panama over toxic cough syrup scandal that killed hundreds

Five jailed in Panama over toxic cough syrup scandal that killed hundreds

Posted Sat 30 Jul 2016 at 4:09am

The medicine had been mixed and distributed by the national health agency. *(ABC)*

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abc.net.au/news/five-jailed-in-panam...

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Five people were sentenced to prison in Panama on Friday over a 2006 poison cough syrup scandal in which hundreds of people died after unwittingly ingesting a toxic compound found in antifreeze.

The verdict capped years of investigation and a convulsion of shock at the many deaths in this small Central American nation.

Officials say 400 people died when they drank the adulterated cough syrup, which had been mixed and distributed by the national health agency using an ingredient supplied by a private company, Medicom.

Some Panamanian organisations believe

Key points:

- Officials say 400 people died as result of syrup
- Same organisations in Panama say toll could actually be up to 10,000
- Toxic ingredient is used as a solvent, in brake fluid, heating fuel and antifreeze

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My Pikin deaths: Nigerians jailed over poisoned baby drug

17 May 2013

Two Nigerians have been sentenced to seven years in prison over the deaths of at least 80 children who took adulterated teething medicine.

The officials from the company which made the My Pikin syrup were found guilty by a court in Lagos.

After children started dying in 2008, the mixture was found to contain engine coolant.

The judge also ordered that the company be closed and its assets forfeited to the state.

The paracetamol-based syrup, used for treating sore gums, was found to have been contaminated with diethylene glycol, used as an engine coolant.

It caused the babies' kidneys to fail.

My Pikin means "my baby" in Nigerian pidgin, the language widely used in Lagos.

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Maiden Pharmaceuticals: Gambia panel says India firm culpable for cough syrup deaths

21 December 2022

The WHO had advised regulators to stop the sale of the four Indian-made cough syrups

A parliamentary committee in The Gambia has recommended prosecution of the Indian manufacturer of cough syrups suspected of causing the deaths of at least 70 children in the country.

It said Maiden Pharmaceuticals should be held accountable for exporting what it called contaminated medicine.

The WHO had issued an alert in October advising regulators to stop the sale of the syrups.

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Indonesia bans all syrup medicines after death of 99 children

20 October 2022

Indonesia says it's banning the sale and use of all syrup and liquid medicines temporarily

By Frances Mao
BBC News

Cough Syrup Linked to 20 Kids' Deaths Was Circulating for Months

- Export records show tainted medicine made as early as May 2021
- Indian drug maker defends quality of exports to Uzbekistan

By Zachary Mider and Chris Kay
January 12, 2023, 10:00 PM GMT+1

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An Indian drug maker blamed for the deaths of 20 children in Uzbekistan produced multiple batches of tainted cough syrup over more than a year, according to data from export records and the World Health Organization.

The WHO said this week that 21 batches of cough syrup made by India's Marion Biotech Ltd. were tested by Uzbek authorities and found to contain unsafe levels of two toxic chemicals. Bloomberg News identified some of these batches in separate Indian export records as having been manufactured as early as May 2021 and exported to the Central Asian nation that June. Other batches appear to have been made on more than half a dozen dates and as recently as August 2022.

Asia / Australasia

WHO: contaminated cough syrup made in India found in Western Pacific

- Samples from a batch of imported cough syrup in the Marshall Islands and Micronesia were contaminated with unacceptable amounts of ingredients toxic to humans
- The new alert follows three similar warnings issued last year; the manufacturer of the medicines in the latest alert was India's QP Pharmachem, based in Punjab

Reuters +FOLLOW
Published: 9:36pm, 26 Apr, 2023

Why you can trust SCMP

Samples from a batch of cough syrup, with the product name Guaifenesin syrup TG syrup, were contaminated with unacceptable amounts of diethylene glycol and ethylene glycol. Photo: Shutterstock

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2022: Key Events and Alerts on DEG/EG Contamination

Aug.–Oct. 2022

The Gambia:

- Approx 92 suspect AKI cases in children
- More than **70 deaths** reported
- Four different cough/cold syrups preparations
- All imported products manufactured in India
- Medical Product Alert N°6/2022 on 5 October 2022

Aug.–Oct. 2022

Indonesia:

- Approx 325 cases of suspect AKI in children
- Approx **203 deaths**
- At least thirteen products contaminated with EG
- All products manufactured by 7 different local manufacturers.
- Medical Product Alert N°7/2022 issued on 6 November 2022

Dec. 2022

Uzbekistan

- Unconfirmed reports of between **20 to 65 deaths** of children
- AKI cases suspected to be linked to contaminated syrup.
- Two different product with over22 different batches
- All products were imported & manufactured in India
- Medical Product Alert No1/2023 on 11 January 2023

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2023: Key Events and Alerts on DEG/EG Contamination

April 2023

Marshall Islands & Micronesia

- Contaminated cough syrup detected
- No reports of deaths
- One imported product manufactured in India
- Medical Product Alert No4/2023 issued 25 April 2023

March-July 2023

Cameroon

Contaminated cough syrup detected.

At lease **12 deaths** of children

One Imported product manufactured in India

Medical Product Alert No4/2023 issued 19 July 2023.

June-Aug. 2023

Iraq

Contaminated cough syrup first reported by the media

No reports of deaths

One product with six batches

Imported product manufactured in India

Medical Product Alert No5/2023 issued 7 August 2023.

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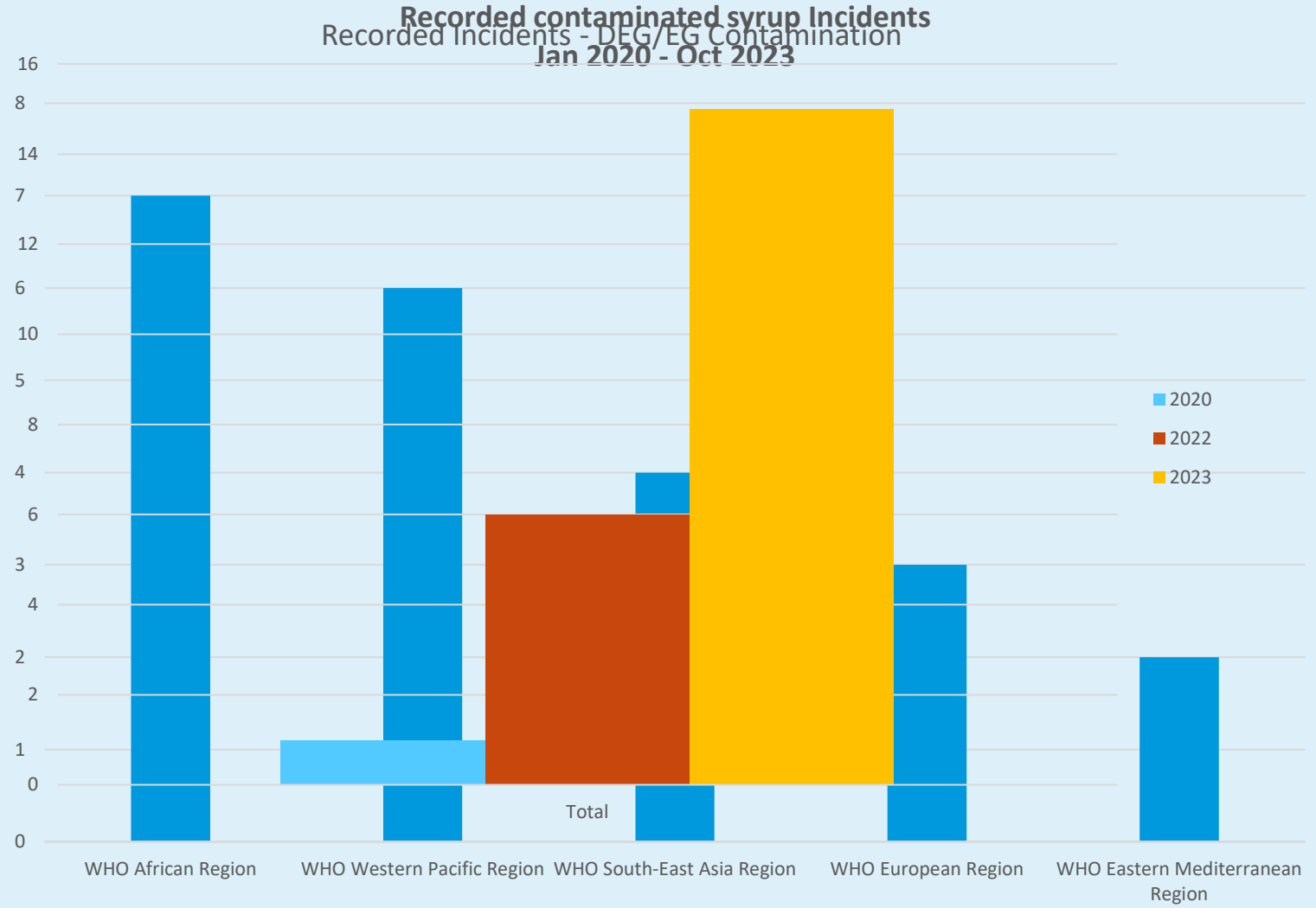
Substandard / Contaminated Syrup medicines

- Number of reported Incidents has increased over the last 3 years.
- Contaminated syrups have been detected in all regions - with exception of the WHO Region of the Americas.
- As of Oct 2023, highest number of incidents in African Region.



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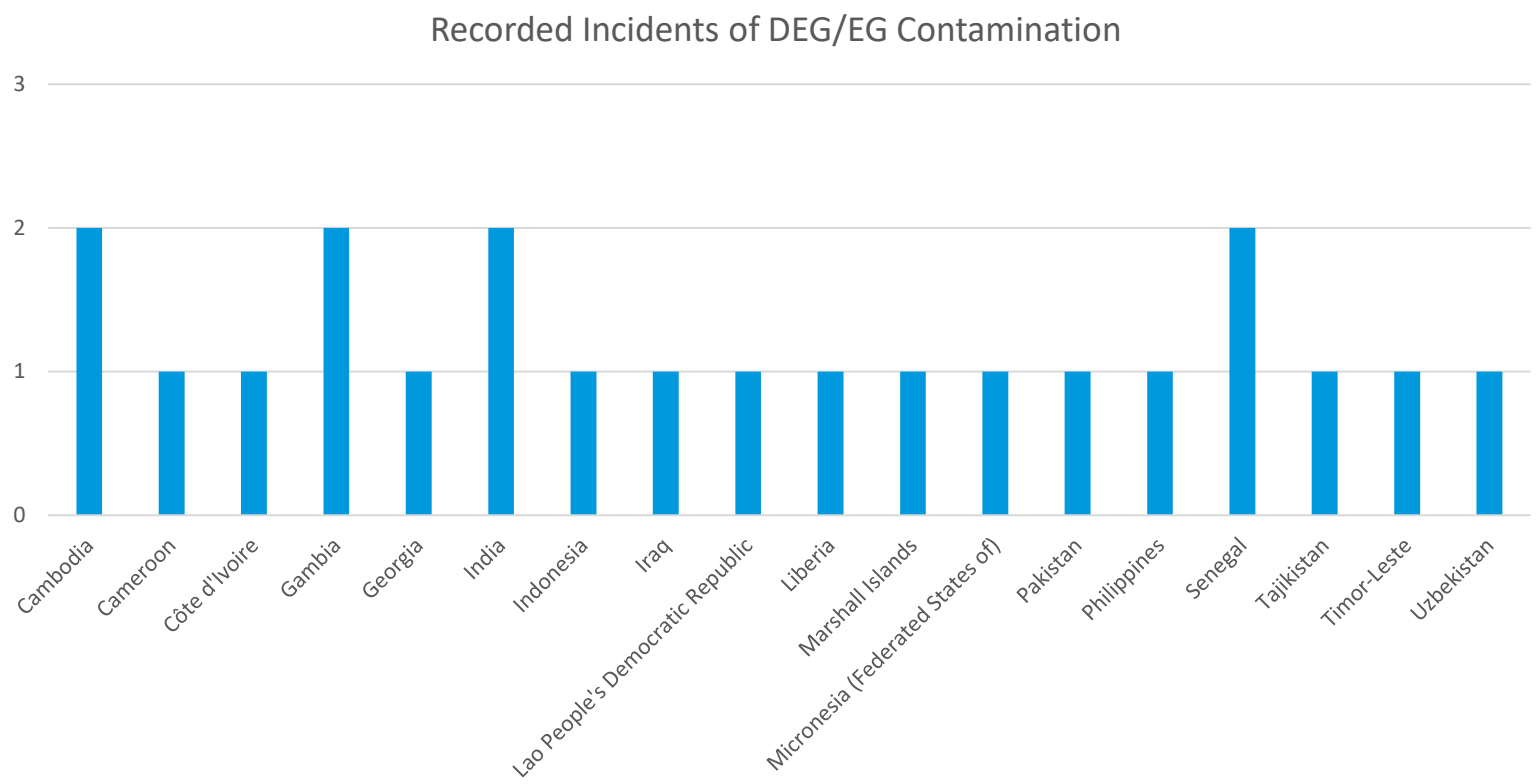
Distribution of recorded Incidents: Jan 2020 – Oct 2023



- 22 reported Incidents of DEG/EG contamination.
- 18 Member States have detected contaminated products.
- 58 unique product batches detected.
- Contaminated products were duly authorised in countries of manufacture.
- Products are traded globally with risk of distribution in illicit and informal markets.

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WHO Medical Product Alert N°6/2023 (Iraq)

Link to alert

World Health Organization

7 August 2023

Medical Product Alert No. 6/2023
Substandard (contaminated) syrup medicines identified in WHO Region of the Eastern Mediterranean

Alert Summary
This WHO Medical Product Alert refers to one batch of substandard (contaminated) COLD OUT syrup (Paracetamol and Chlorpheniramine Maleate) identified in the Republic of Iraq and reported to the World Health Organization (WHO) on 10 July 2023 by a third party. Please refer to the Annex of this Alert for full details of the affected batch of the product.

Paracetamol and chlorpheniramine combination syrups are used to treat and relieve symptoms of the common cold and allergy symptoms.

A sample of the COLD OUT Syrup was obtained from one location in Iraq and submitted for laboratory analysis. The sample was found to contain unacceptable amounts of diethylene glycol (0.25%) and ethylene glycol (2.1%) as contaminants. The acceptable safety limit for both ethylene glycol and diethylene glycol is **no more than 0.10%.**

The stated manufacturer of the affected batch of the product is FOURRTS (INDIA) LABORATORIES PVT. LTD, and the product is stated to be manufactured for DABILIFE PHARMA PVT. LTD. - INDIA. To date, the stated manufacturer and the marketer have not provided guarantees to WHO on the safety and quality of the product.

The product referenced in this Alert may have marketing authorizations in other countries or regions. It may also have been distributed, through informal markets, to other countries.

Please refer to the Annex of this Alert for full details of the affected batch of the product.

WHO has previously published **five Alerts on other contaminated liquid dosage medicines**. Please see Medical Product Alert N°6/2022, Medical Product Alert N°7/2022, Medical Product Alert N°1/2023, Medical Product Alert N°4/2023, and Medical Product Alert N°5/2023.

Risks
Diethylene glycol and ethylene glycol are toxic to humans when consumed and can prove fatal. The substandard batch of the product referenced in this Alert is unsafe and its use, especially in children, may result in serious injury or death. Toxic effects can include abdominal pain, vomiting, diarrhoea, inability to pass urine, headache, altered mental state and acute kidney injury which may lead to death.

Advice to regulatory authorities and the public
If you have the affected product, WHO recommends that you do not use it. If you, or someone you know, has, or may have used the affected product, or suffered an adverse reaction or unexpected side-effects after use, you are advised to seek immediate medical advice from a healthcare professional.

While this Medical Product Alert relates to only one batch of the product (as set forth in the Annex hereto), out of an abundance of caution, WHO recommends increased vigilance and testing in respect of the product in general.

World Health Organization

7 August 2023

WHO requests increased surveillance and diligence within the supply chains of countries and regions likely to be affected by the product. Increased surveillance of the informal/unregulated market is also advised. National regulatory authorities/health authorities are advised to immediately notify WHO of any substandard/falsified products discovered in their respective country.

Manufacturers of liquid dosage forms, especially syrups that contain excipients including propylene glycol, polyethyleneglycol, sorbitol, and/or glycerin/glycerol, are urged to test for the presence of contaminants such as ethylene glycol and diethylene glycol before use in medicines.

Healthcare professionals should promptly report any suspicious or confirmed cases of adverse events linked to the use of contaminated medicines to the National Regulatory Authorities/National Pharmacovigilance Centre.

If you have any information about the manufacture or supply of any contaminated batch of this product, please contact WHO via rapidalert@who.int.

Annex: Batch of Product subject of WHO Medical Product Alert No.6/2023

Product name	COLD OUT syrup
Stated manufacturer	FOURRTS (INDIA) LABORATORIES PVT. LTD
Stated marketer	DABILIFE PHARMA PVT. LTD. - INDIA
Batch	SF001A02
Expiry date	DEC.2024
Identified in	Republic of Iraq
Available photos	

WHO Global Surveillance and Monitoring System for Substandard and Falsified Medical Products
Please visit: https://www.who.int/health-topics/substandard-and-falsified-medical-products, or **e-mail:** rapidalert@who.int

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WHO Medical Product Alerts

Why Are Alerts issued?

- Alerts are in response to detection of an SF product or adverse event arising from a SF medical products where there is:
  - *an immediate and significant threat to public health, or*
  - *has already been linked to adverse events / patient harm, and*
  - *a risk the product is in more then one country/WHO Region*
- Enhanced and risk communication, on a global platform, is appropriate to help detect and remove the products from the market.
  - *Total of 66 Medical Product Alerts issued since 2012.*
  - *Alerts have identified 281 substandard or falsified medical products.*

General observations from Incidents

Delays in associating AKI incidents with potentially contaminated medicines

Reported AKI involve mostly children

Challenges in accessing medical interventions e.g. haemodialyis or antidotes - fomepizole or ethanol

Products involve liquid dosage (mainly paediatric) medicines for treatment of symptoms of cough, cold or fever

Challenges in conducting timely and accurate lab analysis

Common excipients - propylene glycol, polyethylene glycol, glycerin/glycerol or sorbitol solution

Majority of contaminated products manufactured / imported from a few countries

Market withdrawal of the suspected liquid dosage medicines leads to decline in number of reported AKI cases

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Possible causes – not all confirmed

There is significant global public health risk unless causes are identified

Contamination of active pharmaceutical ingredients / excipients at point of manufacture of raw material **impacting global supply chain** - propylene glycol, sorbitol or glycerin

Falsification (including adulteration) of active pharmaceutical ingredients / excipients at some point **in the global supply chain**

Accidental / intentional **substitution of industrial grade** propylene glycol / glycerin / sorbitol solution in place of pharmaceutical grade product, in supply chain or at the manufacturing site

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What is the WHO doing?

Prevention

- Strengthen capacity of NRAs in Market Surveillance and Control
- WHO good manufacturing practices for pharmaceutical excipients draft working document
- Member State mechanism working group F on strengthening supply chain of excipients at risk
- New WHO Pharmaceutical Starting Materials Certification Scheme (SMACS)
  - *Pharmaceutical starting materials, obtained through chemical synthesis*
  - *A provision for alternative quality assurance systems and self-assessment by the manufacturers of starting materials.*
  - *May be linked to an inspection by a national authority other than the one in the country of manufacture.*
  - *A Member State may opt to participate solely to control the importation of starting materials*
  - *Manufacturers should have a system in place to notify customers and regulatory authority in case of defects*
- Research into global market for at risk excipients - propylene glycol, polyethylene glycol, glycerin/glycerol or sorbitol solution

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What is the WHO doing?

Detection

- Improve regional capacity for testing
- Development and inclusion of screening or detection and testing methods for DEG/EG in raw materials and medicines
  - Guidance for selection of technologies
  - Tiered approach for the detection of diethylene glycol and ethylene glycol in liquid preparations for oral use for inclusion in Ph.Int.
  - Comprises a screening for non-compliance by thin-layer chromatography and a confirmatory testing by gas chromatography
- Support continued post market surveillance programs – sampling and testing

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What is the WHO doing?

Response

- Support Member States investigations into production and distribution of contaminated products
- Identify manufacturers, supply-chain vendors, repackagers, distributors
- Encourage reporting of adverse events and monitoring of potential signals as unusual spikes
- Issue Medical Product Alerts

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Overall lessons learnt

Public awareness and risk communication is critical

Market Surveillance to detect DEG/EG contamination. Some countries have reported levels below or just above the acceptable minimum limits

Limited access to laboratories for confirmation & quantification of contamination

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… and the victims always have faces and names

Rayvan - can now barely move

Source: https://www.abc.net.au/news/2022-12-22/indonesia-children-acute-kidney-injury-contaminated-medicine/101798484?utm_campaign=newsweb-article-new-share-null&utm_content=link&utm_medium=content_shared&utm_source=abc_news_web

Nadira – 17 months

Source: Indonesia syrup deaths: Parents demand accountability as toll rises - BBC News

Musa – 20 months

Source: Gambia cough syrup scandal: Mothers demand justice - BBC News

World Health Organization

Thank you

For more information, please contact:
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