# Epidemic of Pediatric Deaths From Acute Renal Failure Caused by Diethylene Glycol Poisoning

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**Context.—**Contaminated pharmaceutical products can result in substantial morbidity and mortality and should be included in the differential diagnosis of deaths of unknown origin.

**Objective.—**To investigate an outbreak of deaths among children from acute renal failure in Haiti to determine the etiology and institute control measures.

**Design.—**Case-control study, cohort study, and laboratory toxicologic evaluation.

**Setting.—**Pediatric population of Haiti.

**Participants.—**Cases were defined as Haitian residents younger than 18 years with idiopathic anuria or severe oliguria for 24 hours or longer. Febrile hospitalized children without renal failure were enrolled as control subjects.

**Main Outcome Measure.—**The odds of exposure to suspected etiologic agents among cases and controls.

**Results.—**We identified 109 cases of acute renal failure among children. The clinical syndrome included renal failure, hepatitis, pancreatitis, central nervous system impairment, coma, and death. Of 87 patients with follow-up information who remained in Haiti for treatment, 85 (98%) died; 3 (27%) of 11 patients transported to the United States for intensive care unit management died before hospital discharge. A locally manufactured acetaminophen syrup was highly associated with disease (odds ratio, 52.7; 95% confidence interval, 15.2-197.2). Diethylene glycol (DEG) was found in patients' bottles in a median concentration of 14.4%. The median estimated toxic dose of DEG was 1.34 mL/kg (range, 0.22-4.42 mL/kg). Glycerin, a raw material imported to Haiti and used in the acetaminophen formulation, was contaminated with 24% DEG.

**Conclusions.—**An epidemic of severe systemic toxicity and deaths from DEG-contaminated acetaminophen syrup occurred in Haiti. Good manufacturing practice regulations should be used by all pharmaceutical manufacturers to prevent such tragedies.

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A complete list of the Acute Renal Failure Investigation Team appears at the end of this article.

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ACUTE RENAL failure is an unusual cause of death among children. Where infant and child mortality rates are high, the common causes of death are acute respiratory illness, diarrhea, dehydration, malnutrition, and sepsis.[1-3] Increased rates of death from other causes may not be recognized in these settings unless the diseases are unusual or the outbreaks are large. Between November 1995 and May 1996, approximately 32 children with idiopathic acute renal failure were admitted to the University General Hospital in Port-au-Prince, Haiti, whereas no children had been admitted with this diagnosis in the preceding 5 years; 31 of these children died. An intensive investigation involving members of the Ministry of Health of Haiti, the University General Hospital in Port-au-Prince (HUEH), the Pan American Health Organization (PAHO), the Centers for Disease Control and Prevention (CDC), the Caribbean Epidemiology Center, and other local and international organizations was initiated in June 1996 to determine the cause of the outbreak, institute control measures, and evaluate their effectiveness.

**For editorial comment see p 1215.**

## METHODS

### Case Definition

We defined cases as idiopathic anuria or severe oliguria for 24 hours or longer diagnosed on or after October 1, 1995, in a Haitian resident younger than 18 years. We evaluated potential causes of re-

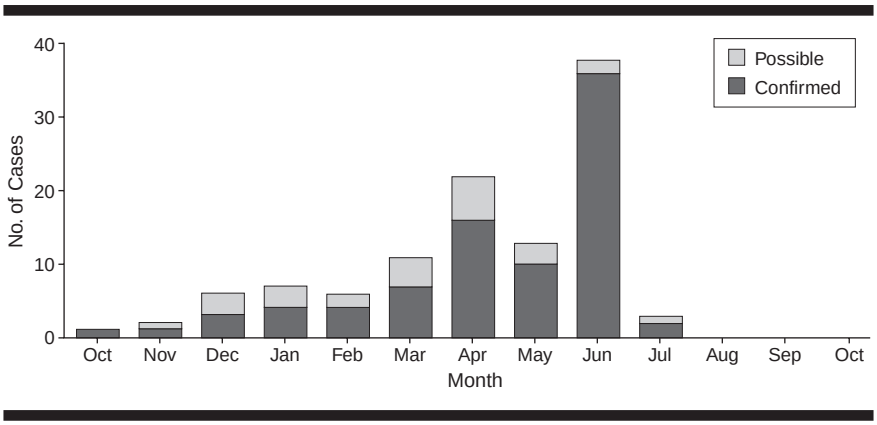


Figure 1.—Month of hospital admission for children with acute renal failure, Haiti, October 1995-October 1996.

nal failure by maternal interviews and hospital chart information. We considered a case confirmed if either a maternal interview or a hospital chart review was completed and the case definition was fulfilled. If the chart review or the maternal interview suggested a diagnosis that was not supported by historical, clinical, or laboratory findings or that lacked sufficient detail to exclude a known etiology of renal failure, we considered the case only possible. We also considered a case possible if neither a maternal interview nor a chart review was completed for a child who otherwise met the case definition. Possible cases were included in the descriptive epidemiology to provide the most sensitive evaluation of the epidemic.

### Case Finding

Cases were identified primarily through the recall of pediatricians at HUEH. No admission or discharge logs were available, and there was no means to systematically search medical records. Cases also were identified through disease surveillance lists collected by the Ministry of Health of Haiti, notifications from private pediatricians, and community-based reporting to field health workers. Cases were included in the case-control study if either a maternal interview or a chart review was completed on or before July 13, 1996, regardless of onset date of illness or admission to the hospital.

### Control Selection

A convenience sample of children hospitalized at HUEH between June 19 and July 2, 1996, was enrolled prospectively as control subjects if they were younger than 18 years, had been hospitalized for any reason other than renal failure, and had a history of fever during their current illness.

### Data Collection

We collected detailed information by maternal interview and chart review to determine the signs and symptoms of illness in the 2 weeks before admission, the progression of disease, and all exposures in the 2 weeks before the onset of anuria, including medications, creams, herbal remedies, baths, and tonics. We also collected information on demographic characteristics of each study subject and the subject's family.

### Toxicology Analysis

Diethylene glycol (DEG) was detected in the contaminated syrups by several separate confirmatory analytical techniques. The sodium adduct ($[M+Na]^+$, mass-to-charge ratio, 129) of DEG was detected in the implicated syrups and standards, but not in a control syrup, by continuous-infusion electrospray ionization mass spectrometry with a magnetic sector mass spectrometer (model 70-4SE, Micromass, Manchester, England) using a 0.1% acetic acid–methanol (1:1) solvent system. These results were confirmed by accurate mass fast-atom bombardment mass spectrometry, high-performance liquid chromatography/electrospray ionization mass spectrometry/mass spectrometry (HPLC/ESI-MS/MS), gas chromatography–mass spectrometry, and proton and tagged stable carbon isotope nuclear magnetic resonance spectroscopy.

To quantify the percentage of DEG (vol/vol) in implicated syrups, we developed a method for internal standard calibration using isotope dilution technique and a triple quadrupole mass spectrometer (model TSQ700, Finnigan MAT, San Jose, Calif). Samples and standards were prepared by dissolving 100 µL of syrup or 10 µL of deuterated DEG in 4 mL of methanol and were analyzed by HPLC/ESI-MS/MS of the ammonium adduct ($[M+NH_4]^+$) of DEG. A calibration curve was constructed by plotting the response factor against the percentage of DEG, and the equation from a linear regression analysis was used to quantify the percentage of DEG in the acetaminophen preparations. The limit of detection (3 SDs) of the method was determined to be 0.7% DEG (vol/vol) in the formulation, and the average coefficient of variation of the method calculated from repeat measurements was 16%.

### Toxic Dose Estimates

The DEG dose per kilogram of body weight for individual patients was estimated by multiplying the percentage of DEG in bottles provided by the child's parent by the volume missing from the bottle and dividing by the weight of the child as documented in the hospital admission record. For children without a documented weight, we estimated age-appropriate weights by applying the median weight-for-age $z$ score from children whose weight was documented.[4] For children who reportedly shared the contaminated medication with another person, we assumed that the affected child consumed the entire quantity missing from the bottle. This method provides an estimate of the maximum possible dose ingested; the actual ingested dose could have been any amount less than the calculated dose.

### Cohort Study

Between June and September 1996, we enrolled in a longitudinal, prospective cohort study any child who presented to HUEH without renal failure who was younger than 15 years and had a history of consuming acetaminophen syrup from a DEG-contaminated lot. Children were included in the cohort analysis if they could provide a medication bottle with a legible lot number or expiration date for verification. A detailed history and physical examination were conducted for each child. If the last dose of contaminated medication was consumed less than 14 days before the interview, a blood sample was drawn for renal, hepatic, pancreatic, and hematologic function tests. At least 1 visit was scheduled at 4 weeks after the last exposure to evaluate for evolving signs or symptoms of toxic effects. Because the DEG concentration was not measured from the bottle of each cohort child, the median DEG concentration from patient bottles was used along with the measured ingested volumes for each child in the cohort to determine the ingested DEG dose. Weights of children were measured or estimated by applying the mean weight-for-age $z$ score of the weighed children in the cohort to those who were not weighed.

### Statistical Analysis

Potential risk factors were assessed using odds ratios (ORs) and 95% confidence intervals (CIs). Only individuals

who could state the brand name of a medication or who could provide a medication bottle were considered exposed to that medication. Means were compared using analysis of variance, and proportions compared using Mantel-Haenszel $\chi^2$ test for significance.

## RESULTS

### Epidemic Description

One hundred nine children were identified who fulfilled the case definition; 87 were confirmed and 22 were possible cases. Cases were classified as possible for the following reasons: neither a maternal interview nor a chart review (7); insufficient information to include or exclude any etiology (8); and another diagnosis stated in the chart but historical, clinical, or laboratory findings did not support that diagnosis (typhoid fever [2], hemolytic uremic syndrome [3], meningitis [1], and dehydration [1]). Sixty-five patients (60%) were male. Only 1 set of siblings was affected; none of the other case patients was related. Cases began to present in the fall of 1995 and reached a peak in June 1996; the last case detected occurred in July 1996 (Figure 1). Children ranged in age from 1 month to 13 years; 87 affected children (80%) were younger than 5 years and 45 (41%) were younger than 2 years. Cases were identified from 5 of 9 geopolitical units, termed *departments*, within Haiti; 69% of case patients resided in the capital city of Port-au-Prince.

### Case-Control Analysis

Sixty-three of 109 patients and 52 controls fulfilled inclusion criteria for the case-control analysis. The remaining 46 patients were excluded from the case-control analysis because information from the maternal interview or the hospital chart review was not available by the date of the analysis, July 13, 1996, as defined in the "Case Finding" section. Patients were similar to controls in age and sex distribution, but had consumed more medications in the 2 weeks before admission (Table 1).

In a univariate analysis, consumption of a locally manufactured acetaminophen syrup preparation marketed under the brand names Afebril and Valodon was highly associated with disease. The OR for exposure to either product in the 2 weeks preceding the date of admission was 52.7 (95% CI, 15.2-197.2). No other medication exposure was statistically associated with disease; however, the laboratory analysis did reveal that other medications produced by the same manufacturer were contaminated with DEG. When exposure was defined as including any DEG-contaminated medication (by laboratory measure or appropriate brand and lot number), the OR for exposure was 44.2 (95% CI, 13.4-156.6).

Table 1.—Demographic and Medication Data for Case and Control Subjects

| Characteristic | All Case Patients (n=109) | Case-Control Study Subjects | | |
|---|---|---|---|---|
| | | Patients (n=63) | Controls (n=52) | *P* Value |
| Mean age (range) | 38.2 mo (1 mo-13 y) | 37.1 mo (3 mo-13 y) | 40.0 mo (2 mo-15 y) | .69 |
| Male, No. (%) | 65 (60) | 41 (65) | 25 (48) | .07 |
| Mean No. of medications by history (range) | 3.6 (1-10) | 3.8 (1-9) | 2.0 (0-5) | <.001 |
| Mean No. of medications collected (range) | 4.0 (0-18) | 5.0 (0-18) | 2.3 (0-13) | <.001 |

Table 2.—Clinical and Laboratory Findings Among Patients

| Findings | Median (Range)* | No. Abnormal (No. Examined) | Proportion Abnormal, % |
|---|---|---|---|
| Clinical | | | |
| Edema | . . . | 34 (45) | 75.6 |
| Dehydration | . . . | 3 (45) | 6.7 |
| Dilated pupils | . . . | 21 (40) | 52.5 |
| Hepatomegaly | . . . | 29 (50) | 58.0 |
| Clonus | . . . | 5 (10) | 50.0 |
| Facial palsy | . . . | 3 (10) | 30.0 |
| Laboratory (normal values) | | | |
| White blood cell count (<15.0×10$^9$/L) | 13.0 (4.2-37.1) | 17 (47) | 36.2 |
| Hemoglobin (>105 g/L) | 92 (50-140) | 35 (49) | 71.4 |
| Platelet count (<400×10$^9$/L) | 380 (90-999) | 11 (25) | 44.0 |
| Alanine aminotransferase (<30 U/L) | 95 (37-550) | 8 (8) | 100.0 |
| Aspartate aminotransferase (<40 U/L) | 140 (64-447) | 8 (8) | 100.0 |
| Amylase (<125 U/L) | 495 (115-932) | 5 (6) | 83.3 |
| Lipase (<180 U/L) | 423 (19-801) | 2 (3) | 66.7 |
| Serum urea nitrogen (<13.9 mmol/L [39 mg/dL]) | 24.6 (7.1-51.8) [69 (20-145)] | 47 (48) | 95.8 |
| Creatinine (<88.4 µmol/L [1.0 mg/dL]) | 592 (203-1459) [6.7 (2.3-16.5)] | 49 (49) | 100.0 |

*Ellipses indicate data not applicable.

### Clinical Manifestations and Outcome of Cases

Parents of 86 case patients could describe the symptoms that led to the use of the contaminated acetaminophen liquid; these included fever in 81 (94%), vomiting in 29 (34%), diarrhea in 25 (29%), cough in 19 (22%), and abdominal pain in 3 (4%). Subsequent to ingesting the medication, parents noted various symptoms in their children, including anuria in 80 (95%), edema in 40 (48%), abdominal pain in 23 (27%), altered consciousness in 17 (20%), oliguria in 10 (12%), and dyspnea in 9 (10%).

Signs and symptoms observed in the hospital were inconsistently noted in the charts; therefore, the proportion of all patients presenting with each sign or symptom could not be established. By definition, all the case patients had acute renal failure. One patient was in polyuric renal failure at admission and subsequently developed anuria; all other patients had either anuria or severe oliguria at the time of admission. Other manifestations of toxic effects included hepatitis, pancreatitis, and severe neurological manifestations (eg, encephalopathy, optic neuritis, minimally reactive or fixed dilated pupils, unilateral facial paralysis, respiratory failure requiring mechanical ventilation, and coma) (Table 2). A detailed description of the clinical manifestations, evaluation, and management of these children is the subject of a separate report.

Of 98 children who remained in Haiti throughout their illness, 11 were in extremis when taken from the hospital by their families and were lost to follow-up. Of the remaining 87 children, 85 (98%) died. Eleven children were transported to the United States for intensive care management, including hemodialysis or peritoneal dialysis; of these, 1 died during air transport and 2 died during hospitalization. Of the 8 surviving children, 7 recovered full renal function; 1 child developed chronic renal failure requiring chronic ambulatory peritoneal dialysis. The 11 children transported to the United States were not different from the 98 who remained in Haiti with respect to age, dose of DEG ingested, or interval between ingestion and presentation to the hospital. They were selected based only on the availability and logistics of transportation to the United States.

Table 3.—Laboratory Findings Among Cohort Study Subjects

| Findings (Normal Values) | Median (Range) | No. Abnormal (No. Examined) | Proportion Abnormal, % |
|---|---|---|---|
| Hemoglobin (>105×10⁹/L) | 105 (92-142) | 6 (13) | 46.0 |
| Platelet count (<400×10⁹/L) | 480 (60-720) | 5 (8) | 62.5 |
| Alanine aminotransferase (<30 U/L) | 25 (11-50) | 2 (13) | 15.4 |
| Aspartate aminotransferase (<40 U/L) | 52 (11-86) | 10 (13) | 76.9 |
| Amylase (<125 U/L) | 165 (29-375) | 10 (14) | 71.4 |
| Serum urea nitrogen (<13.9 mmol/L [39 mg/dL]) | 4.3 (2.5-6.1) [12 (7-17)] | 0 (11) | 0 |
| Creatinine (<88.4 µmol/L [1.0 mg/dL]) | 97.2 (69.8-122.0) [1.1 (0.79-1.38)] | 8 (11) | 72.7 |

### Toxicologic Analysis

Samples of the acetaminophen syrup were analyzed to determine the toxic substance contained therein. Diethylene glycol, a known human toxicant, was identified in bottles from patients, unopened bottles purchased in pharmacies, and retained quality control samples from the manufacturer. Among 36 contaminated patient bottles tested, the median DEG concentration was 14.4% (range, 1.2%-19.6%). Among 32 patients for whom a maximum possible ingested dose could be estimated, the median estimated DEG dose consumed was 1.34 mL/kg (range, 0.22-4.42 mL/kg); 12 children (37.5%) consumed an estimated maximum DEG dose less than 1.0 mL/kg.

### Diethylene Glycol Exposure

A detailed medication history or bottle of medication was available for 82 of 109 affected children. A bottle of the acetaminophen syrup was collected from 50 of these, and an additional 31 had exposure documented by history. Only 1 child had no history of exposure to either medication. Among 54 children for whom the timing of acetaminophen syrup consumption was clearly given, the median time from the first dose to onset of oliguria or anuria was 6 days (range, 1-12 days). Of 7 children who had a definite history of stopping the medication before the onset of oliguria or anuria, the median interval between stopping and noting a change in urinary frequency was 4 days (range, 2-8 days). Although other medications manufactured by the same company were also contaminated with DEG, only 1 patient consumed any other contaminated medication. The medication contained only 1.2% DEG, and this patient also consumed the acetaminophen syrup with a DEG concentration of 17.2%. Among control subjects, only 2 consumed any medications contaminated with DEG. An 8-month-old control subject consumed an estimated DEG dose of 0.4 mL/kg in the form of acetaminophen drops contaminated with 5% DEG, and an 11-month-old control subject consumed an iron supplement produced by the manufacturer that was contaminated with an unknown proportion of DEG.

### Cohort Analysis

Forty-nine well children who ingested a DEG-contaminated lot of acetaminophen syrup were enrolled in a prospective cohort study and followed up for a median of 87 days (range, 19-175 days) after the last dose of acetaminophen syrup. If the date of last ingestion was unknown, the follow-up period began with the first clinical visit. The median age of children was 45 months (range, 1-154 months), and the median ingested DEG dose among 17 children was 0.67 mL/kg (0.05-2.48 mL/kg). All 49 children survived through the follow-up period, and none developed overt signs or symptoms of DEG toxicity; however, numerous children had laboratory evidence of subclinical toxic effects (Table 3).

### Risk Factors for Acute Renal Failure

One hundred thirty-eight children from both the case-control study and the cohort group who consumed acetaminophen syrup from a DEG-contaminated lot were included in an analysis of risk factors for disease. The mean age of children who became ill was 39.5 months compared with 52.1 months among children who did not ($P$=.05). Cases were more likely to have taken the acetaminophen syrup for symptoms of diarrhea (OR, 4.3; 95% CI, 1.7-10.9) or vomiting (OR, 8.8; 95% CI, 3.7-21.8) than were children who did not develop symptoms of DEG toxicity. Among 49 individuals for whom we could estimate the DEG dose ingested per kilogram, children who became ill consumed a mean dose of 1.34 mL/kg, compared with 0.84 mL/kg among those who did not ($P$=.04); however, there was considerable overlap in the range of doses ingested (Figure 2).

### Traceback Investigation

A traceback investigation at the manufacturer revealed that glycerin, used in the formulation of these syrups, was contaminated with 24% DEG. The glycerin had been imported to Haiti through distributors in Europe from a manufacturer in China. It is unknown how and at which point the contamination occurred or if other countries received DEG-contaminated glycerin.

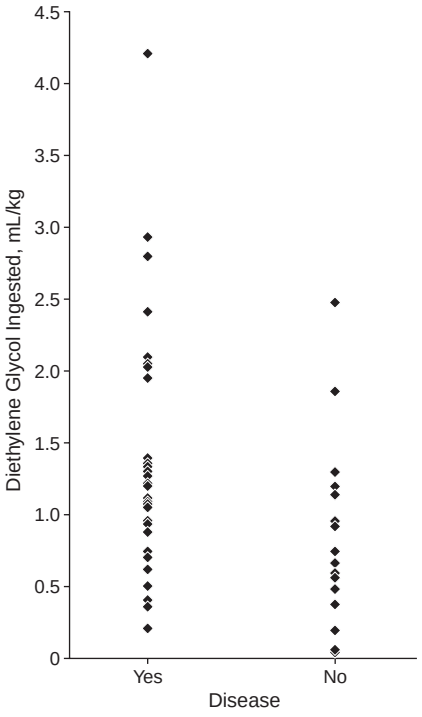


Figure 2.—Maximum concentration of diethylene glycol ingested among ill and well persons exposed to a contaminated acetaminophen syrup.

The manufacturer's formulation of acetaminophen syrup calls for 50% glycerin by volume, resulting in a predicted DEG concentration of 12% in the final product. The DEG-contaminated glycerin was used to produce 3 lots of the acetaminophen syrup for an estimated total volume of 1900 L of syrup; these lots were packaged into 12 000 to 15 000 125-mL bottles of DEG-contaminated syrup with acetaminophen syrup. Based on the manufacturer's production records, we estimate that 38 lots of 15 other liquid preparations were also prepared over the 4-month period when the DEG-contaminated glycerin was in use. The concentration of glycerin in these 15 products ranged from 0.5% to 53%, resulting in predicted DEG concentrations of the marketed products from 0.1% to 12.7%.

### Identity Testing of Glycerin

Infrared spectroscopy is one in a panel of tests recommended in the *US Pharmacopeia* to characterize glycerin. Infrared spectroscopic tests conducted by the US Food and Drug Administration (FDA) on samples of DEG-contaminated glycerin failed, when used alone, to detect the DEG. Application of the entire test panel recommended by the *US Pharmacopeia*, however, would

have detected the contamination. Both gas chromatography and mass spectrometry alone were able to distinguish the glycerin as contaminated with DEG.

### Public Health Interventions

On June 22, 1996, the Haitian Ministry of Health issued a public health warning about the association of the acetaminophen syrup with acute renal failure and prohibited the sale of the 2 products, Afebril and Valodon. Public information campaigns were conducted through radio, television, newspapers, flyers to schoolchildren, and notices to medical societies. The manufacturer issued a recall of all liquid medications that it produced. In the week following the public announcement, 7 additional children were identified with acute renal failure; all had consumed the acetaminophen syrup prior to the announcement. Only 3 additional cases were identified in the ensuing weeks (Figure 1).

## COMMENT

This investigation identified DEG-contaminated acetaminophen syrup as the cause of a large outbreak of acute renal failure deaths among children in Haiti.[5] Diethylene glycol, a known human toxicant, contaminated a shipment of glycerin imported to Haiti from China through Europe. The glycerin was used in numerous locally manufactured liquid pharmaceutical products, including acetaminophen syrup marketed under 2 brand names, Afebril and Valodon; consumption of either of these products was highly associated with disease. Withdrawal of these products from the market resulted in an abrupt cessation of cases.

Although 17 liquid medications were likely contaminated with DEG, only DEG-contaminated acetaminophen syrup was epidemiologically associated with illness. There may be several reasons for this finding. Acetaminophen may provide an additive or potentiating effect for DEG toxicity since both are toxic to the liver and may alter the metabolism of DEG. Some of the children for whom we did not identify an exposure to either proprietary formulation of acetaminophen syrup may have been exposed to other DEG-contaminated medications; however, we were unable to document this by bottle collection or by the patient's history. The DEG concentration in the acetaminophen syrup was greater than that of 14 other products and equivalent to the concentration in the remaining 2 contaminated products (polyvitamin and iron preparations), which would likely have been consumed in smaller amounts than acetaminophen. Finally, children who developed clinical toxic effects were more likely than those without clinical toxic effects to have taken the acetaminophen syrup for diarrhea or vomiting. Preceding gastroenteritis may contribute to DEG absorption or enhance toxic effects through other means.

Table 4.—Summary of Diethylene Glycol (DEG) Outbreaks

| Year | Country | Deaths | Route | DEG Vehicle | DEG Source |
|---|---|---|---|---|---|
| 1937[8] | United States | 105 | Oral | Sulfanilamide elixir | DEG excipient |
| 1967[9] | South Africa | 7 | Oral | Liquid sedatives | Unknown |
| 1985[10] | Spain | 5 | Topical | Sulfadiazine | DEG excipient |
| 1986[11] | India | 14 | Oral | Glycerin | Industrial-grade glycerin |
| 1990[12] | Nigeria | 47 | Oral | Acetaminophen | DEG replaced propylene glycol |
| 1990-1992[13] | Bangladesh | 51 | Oral | Acetaminophen | DEG replaced propylene glycol/glycerol |
| 1992[14] | Argentina | 26 | Oral | Propolis | DEG excipient |

Although acute anuric renal failure was recognized as the hallmark sign of DEG ingestion, exposure resulted in severe systemic toxic effects. Therefore, dialysis alone would likely have been insufficient to avert mortality. Because renal failure from DEG is usually reversible, children may survive this toxic effect when provided with multisystem intensive care support, including mechanical ventilation, parenteral nutritional, and fluid management, in addition to dialysis.

Through a cohort study of DEG-exposed children, we identified individuals who had laboratory-based evidence of toxic effects but no clinical findings. Although the cohort study involved a limited number of patients, the doses ingested by these children were in a similar range as those ingested by the children who experienced DEG toxicity, indicating that there are other risk factors or significant individual variation that would predict the development of disease. This observation agrees with the findings of the only other cohort study of exposed individuals, which also noted that the fatal and nonfatal dose ranges overlapped considerably.[6] Age may be 1 risk factor since it was independently associated with disease. However, because the children in the cohort study were a self-selected rather than a randomly selected group of all exposed children, a selection bias may have been present.

The mechanism of DEG toxicity in humans is not well characterized, and minimum toxic dose ranges have not been well established. A DEG dose of 1 mL/kg has been suggested as the minimum toxic dose[7]; however, there is little evidence to support this. This study documented that toxic doses are often less than 1 mL/kg; therefore, clinical outcome should not be predicted based on this cutoff value. The intervals from the first DEG exposure and the last DEG exposure to onset of illness indicate that, if disease is going to occur, it will present within a short time after exposure.

The public health impact of a rapid investigation and resultant interventions described in this report emphasizes the importance of disease surveillance and early identification of outbreaks. From the company's manufacturing records, visits to randomly selected pharmacies, and an inventory of the acetaminophen syrup bottles turned over by pharmacies to the national police, we estimate that at least 15 000 bottles of DEG-contaminated acetaminophen syrup were produced, and 40% of bottles on the market at the time of the investigation were from contaminated lots. Approximately 60% to 70% of the contaminated lots probably had already been sold; therefore, the 109 identified cases represented 60% to 70% of the expected cases. By these estimates, between 45 and 75 additional cases of DEG toxicity are estimated to have been averted by the intervention.

Although this outbreak was an unusual occurrence, it is not unique and could occur again. Poisoning with DEG has most frequently been observed in outbreak situations rather than as sporadic cases and has usually been observed in association with contamination of ingestible pharmaceutical products (Table 4).[8-14] The first outbreak described was the Massengill disaster of 1937 in the United States, when DEG was used as the excipient in a liquid sulfanilamide preparation.[6,15] At that time DEG was not known to be highly toxic to humans, and no safety evaluations were conducted before marketing the product. One hundred five deaths, predominantly among adults, resulted from ingestion. Recent outbreaks of acute renal failure have been caused by DEG-contaminated acetaminophen liquid preparations in Nigeria and Bangladesh.[12,13] In both settings, the contaminated raw material was propylene glycol. Glycerin contaminated with DEG has been implicated in only 1 other outbreak; in 1986 orally administered DEG-contaminated glycerin was used in an Indian hospital for control of intracranial or intraocular pressure and resulted in 14 deaths.[11]

This outbreak highlights the challenges in developing countries where there may not be adequate regulation, enforcement, or strict implementation of cur-

rent good manufacturing practice regulations in the pharmaceutical sector. Not only should strict quality control procedures be required in all countries where pharmaceutical products are manufactured, but these procedures must be consistently and fully applied, otherwise an outbreak such as this could occur even in countries where quality control procedures are usually strictly applied. The Haitian government and local industry representatives are working to propose and enact legislation and industry norms to avert such a disaster in the future. As noted, infrared spectroscopy alone may not always identify DEG contamination of glycerin. For this reason, it is important that manufacturers verify the test results on certificates of analysis received from their suppliers.

Special problems exist in developing countries where the technology to apply *US Pharmacopeia* standards may not be available or may be too costly to use. To address this problem, the FDA and the World Health Organization (WHO) have worked to develop and adapt a low-cost, safe, simple-to-use thin-layer chromatography technique appropriate for identification of ethylene and DEG in raw materials such as glycerin and in finished liquid products.[16] The technique can detect DEG to a concentration of less than 1% and is undergoing field testing. In November 1996, a working group including representatives from FDA, WHO, PAHO, CDC, and the pharmaceutical industry met to discuss this and other strategies aimed at preventing disease outbreaks from contaminated pharmaceutical products (M. McGeehin, MD, oral communication, February 8, 1998). It is likely that disasters such as these will continue to occur until strict quality control procedures are used consistently by all pharmaceutical manufacturers and until countries around the world adopt and enforce regulations that ensure the safety of pharmaceutical products.

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