Clinical Features of Reported Ethylene Glycol Exposures in the United States

Meghan A. Jobson1,2, Susan L. Hogan1,2, Colin S. Maxwell3, Yichun Hu1,2, Gerald A. Hladik1,2, Ronald J. Falk1,2, Michael C. Beuhler4, William F. Pendergraft, III1,2 *

1 University of North Carolina (UNC) School of Medicine, Chapel Hill, North Carolina, United States of America, 2 UNC Kidney Center, Division of Nephrology and Hypertension, Department of Medicine, Chapel Hill, North Carolina, United States of America, 3 Department of Biology, Duke Center for Systems Biology, Duke University, Durham, North Carolina, United States of America, 4 Carolinas Poison Center, Carolinas Medical Center, Charlotte, North Carolina, United States of America

* wfp3@med.unc.edu

Abstract

Background
Ethylene glycol is highly toxic and represents an important cause of poisonings worldwide. Toxicity can result in central nervous system dysfunction, cardiovascular compromise, elevated anion gap metabolic acidosis and acute kidney injury. Many states have passed laws requiring addition of the bittering agent, denatonium benzoate, to ethylene glycol solutions to reduce severity of exposures. The objectives of this study were to identify differences between unintentional and intentional exposures and to evaluate the utility of denatonium benzoate as a deterrent.

Methods and Findings
Using the National Poison Data System, we performed a retrospective analysis of reported cases of ethylene glycol exposures from January 2006 to December 2013. Outcome classification was summed for intentionality and used as a basis for comparison of effect groups. There were 45,097 cases of ethylene glycol exposures resulting in 154 deaths. Individuals more likely to experience major effects or death were older, male, and presented with more severe symptoms requiring higher levels of care. Latitude and season did not correlate with increased exposures; however, there were more exposures in rural areas. Denatonium benzoate use appeared to have no effect on exposure severity or number.

Conclusion
Deaths due to ethylene glycol exposure were uncommon; however, there were major clinical effects and more exposures in rural areas. Addition of denatonium benzoate was not associated with a reduction in exposures. Alternative means to deter ingestion are needed. These findings suggest the need to consider replacing ethylene glycol with alternative and less toxic agents.
Introduction

Ethylene glycol is a synthetic, colorless, and odorless liquid that tastes sweet and is used primarily to produce plastic containers and polyester fibers and secondarily as the main component in engine antifreeze [1]. Despite its utility, ethylene glycol is highly toxic and represents an important and persistent cause of intentional and unintentional poisonings worldwide [1–5]. Toxicity occurs after enzymatic conversion of the parent alcohol to glycolic acid and oxalic acid, which both produce numerous clinical manifestations, including confusion, nausea, vomiting, central nervous system dysfunction, cardiovascular compromise, elevated anion gap metabolic acidosis, and acute kidney injury [6–9]. Treatment includes supportive care, inhibition of alcohol dehydrogenase with intravenous fomepizole [7,10–12], and renal replacement therapy when there is severe acidemia or end organ injury, including acute kidney injury or severe neurologic impairment [13]. Prior to approval of fomepizole by the FDA in 1997 for the treatment of ethylene glycol poisoning [10], ethanol, used to inhibit alcohol dehydrogenase, was a mainstay of therapy. Ethanol continues to be used worldwide, but serious adverse side effects, including sedation and hypoglycemia, limit its utility [14,15].

In an attempt to limit human and animal exposures to ethylene glycol, denatonium benzoate (commonly Bitrex®), the most bitter-tasting compound known to man, has been added to ethylene glycol in antifreeze to serve as a non-toxic deterrent in many countries, including the United Kingdom, Canada, and the United States [16,17]. The first law in the United States requiring its addition was passed in the state of Oregon in 1991 [18,19]. Sixteen other states followed suit, yet attempts to pass national legislation mandating addition of a bittering agent to engine coolant and antifreeze have failed [20]. In 2012, the Consumer Specialty Products Association announced an agreement with the Humane Society Legislative Fund to voluntarily add this agent; however, previous limited state-specific analysis of the utility of denatonium benzoate showed no reduction in exposures [21–24].

We analyzed all cases of reported ethylene glycol exposures within the National Poison Data System (NPDS) between 2006 and 2013 to determine differences between intentional and unintentional exposures, and to evaluate the utility of denatonium benzoate as a deterrent.

Methods

Setting and Participants

The NPDS, maintained by the American Association of Poison Control Centers (AAPCC), houses case records from the United States Poison Control Network, which receives human and animal poison exposure reports in all 50 states, the District of Columbia, American Samoa, the Federated States of Micronesia, Guam, Puerto Rico, and the U.S. Virgin Islands (S1 Table) [3]. The NPDS is the largest poison-exposure surveillance database in the United States, and is routinely used by the Centers for Disease Control, Food and Drug Administration, Environmental Protection Agency, Consumer Product Safety Commission and Drug Enforcement Agency. In 2006, a real-time data-capture repository was established, which replaced and updated the previous repository. All data analyzed in this report were entered after the new system was put into place. The AAPCC reviewed and approved our request for data, and the Institutional Review Board of Carolinas HealthCare System (CHS) approved this study (CHS IRB File # 04-14-15EX). Data was anonymized and de-identified prior to analysis. All authors vouch for the accuracy and completeness of the data.
Design Overview, Definitions, and Data Analysis

We identified all cases of ethylene glycol exposure in humans within the NPDS from January 1, 2006 to December 31, 2013 using the AAPCC codes for ethylene glycol (automotive products including antifreeze, generic code 051221) or ethylene glycol (excluding automotive, aircraft, or boat products, generic code 052160). All cases that were confirmed as non-exposures or multiple substance exposures and cases outside the United States were excluded from analysis (S2 Fig). Exposures were classified as intentional, unintentional, other, or unknown. Analysis included all exposure types unless otherwise noted.

We ascertained the following demographic characteristics from these data: age, weight in kilograms, date of ingestion, sex, routes of exposure, reason for exposure, clinical effects/complaints, medical interventions, and medical outcomes. Age was calculated using continuous reported variables except for unintentional ingestions by individuals less than 18 years old, which includes additional categorical classifications, including: \( \leq 5 \) years, 6–12 years, teen, and “unknown child” that were included as discrete age categories. Weight values for children under two years old were validated to correct for unit errors (pounds instead of kilograms). This was performed by visualizing weight of all patients under two years old and comparing to 150% of the normal values by age referencing World Health Organization (WHO) growth charts [25]. Outliers were divided by 2.205 to convert pounds to kilograms (S1 Fig). Seasons were defined as spring (March 20th to June 20th), summer (June 21st to September 21st), fall (September 22nd to December 20th), and winter (December 21st to March 19th) as averaged from 2006 to 2013. The route of exposure was most commonly oral. Other routes of exposure include ocular, otic, inhalation/nasal, aspiration, parenteral, dermal, rectal, vaginal, and “unknown.” Cases with a non-oral route of exposure were excluded when measuring the effect of denatonium benzoate on outcomes. The reason for exposure is coded as “unintentional” (an unforeseen or unplanned event), “intentional” (the result of a purposeful action), “other” (malicious as well as contaminant/tampering), “adverse reaction,” or “unknown” (for distributions see S5 Table). Clinical effects are discrete data fields and coded as “related,” “unknown if related,” or “not related.” These reflect the assessment of the specialist in the attribution of that clinical effect to the toxicant in question. There are 131 discrete possible clinical effects associated with each case; “related” and “unknown if related” were grouped as present, and “not related” and “not coded/null” as not present.

We report four common clinical complaints (headache, nausea, vomiting and abdominal pain) and five specific and more serious effects commonly associated with ethylene glycol ingestion (seizures (single and multiple), seizures (status epilepticus), coma, anion gap acidosis, and kidney damage). The clinical effect “seizures (single/multiple)” was defined if either “seizures, single” or “seizures, multiple” was coded as present. The clinical effect “anion gap acidosis” was defined if either “elevated anion gap” or “metabolic acidosis” was coded as present. The clinical effect “kidney damage” was defined if any of the following clinical effects were coded as present: “creatinine elevated,” “oliguria,” “anuria,” and “renal failure.” Effects coded as “related” and “unknown if related” were summed for each variable. Previous work indicates that coding of effects can be variable and that it is appropriate to combine similar effects, especially when there is inherent redundancy in the definition of the clinical effect [26,27]. Data extracted from the reported therapies include two common interventions for critically ill patients (intubation and intravenous fluids) and three more specific interventions commonly recommended and administered to patients who have been exposed to ethylene glycol (ethanol, fomepizole, and renal replacement therapy). Therapies coded as “recommended and performed” and “performed” were summed for each variable.
Medical outcomes are reported by the NPDS using the following five mutually exclusive categories: no effect (no signs or symptoms due to exposure), minor effect (signs or symptoms were minimally bothersome and resolved rapidly, e.g., nausea), moderate effect (signs of symptoms were more pronounced, prolonged, or systemic in nature but did not require specific intervention, e.g., acid-base disturbance), major effect (signs or symptoms were life-threatening or required specific intervention, e.g., seizures), death (death resulting from exposure or a direct complication of the exposure), unrelated effect (exposure probably not responsible for the effects), and confirmed non-exposure (exposure later believed to not have occurred). Outcome classification was summed for intentionality (unintentional or intentional; other reasons were excluded for this analysis) and used as a basis for separation and comparison of effect groups. Outcomes were grouped into "minor or no effect," "death or major effects," or "moderate effect" for analysis. The contribution to fatality for death cases was requested; cases were excluded if the AAPCC reviewer did not feel that death was a result of ethylene glycol exposure. Outcomes were assessed overall, by intentionality, and by ICU use.

Statistical Analyses
Categorical data are reported as summed frequency and percentages and compared using chi-square or Fisher’s exact tests as indicated. Continuous data are reported as mean and standard deviation and are compared using a two-tailed unpaired Student’s t-test or an analysis of variance (ANOVA) as indicated. In the case of a significant ANOVA, we applied the Bonferroni correction for multiple comparisons of differences between individual groups. We calculated Pearson correlation coefficients for state incidence proportion compared to population data. Statistical significance was determined using the Bonferroni correction for multiple comparisons (0.05/number of comparison variables) to determine the critical p-value of significance. Predictors of intentional ethylene glycol exposures and of death were examined using multivariable logistic regression models. Results are reported as odds ratios with 95% confidence intervals and p-values. Odds ratios represent the likelihood that subjects with particular characteristics intentionally ingested ethylene glycol (or died). Model discrimination was evaluated using the concordance statistic (C-statistic), with values ranging from 0 to 1, with those approaching 1 determining more discriminating models.

Data analysis was performed using Excel (Microsoft Excel for Mac 2011) and R (R Project for Statistical Computing, version 3.0.2, www.r-project.org) with plyr package (version 1.8) [28]. Statistical analyses were performed and graphs were generated using Prism 5.0 (GraphPad for Mac OS X). To evaluate geographical trends, choropleth maps were generated using ArcGIS ArcMap (Esri Software, version 10.1) using Jenks natural breaks classification method and an Albers projection [29]. GIS files containing state and water feature boundary files were obtained from the National Historical Geographic Information System (NHGIS) and joined with data generated from the NPDS to generate maps [30]. Joined files were exported to Adobe Illustrator CS5 (Adobe) where maps were altered for presentation purposes. Logistic regression analyses were performed using SAS version 9.2 (SAS Institute).

Results
Characteristics of Individuals Exposed to Ethylene Glycol
We identified 45,097 individuals reported to have been exposed to ethylene glycol in the United States between 2006 and 2013 (S2 Fig depicts method for case inclusion and S3 Fig depicts number reported by year). Of these exposures, 7,070 (16%) were intentional, and 38,027 (84%) were unintentional (Table 1). Intentional and unintentional groups were significantly different (p<0.02) for all demographic and clinical variables shown except weight.
(adults), the season during which the ingestion occurred, and headache. Table 1 includes selected features most relevant to toxic alcohol ingestion, but does not include all possible classifications of signs and symptoms, therapies, or outcomes. Males (n = 33,943, 75%) comprised the majority of exposed individuals. Deaths (n = 154, <1%) made up a low percentage of reported clinical outcomes. The following were the most notable enriched characteristics of the intentional ingestion group: older age (mean 39.4 years versus 30.8, p < 0.001), female

| Characteristics          | Total* | Intentional | Unintentional | P-value† |
|--------------------------|--------|-------------|---------------|----------|
| Number of patients, N (%)| 45097 (100) | 7070 (16) | 38027 (84) | —        |
| Age at intoxication      | 30.5 ± 17.23 9512 | 39.4 ± 15.0 6360 | 30.8 ± 17.1 31820 | <0.001‡ |
| Age ≥ 18 at intoxication | 37.4 ± 14.4 32841 | 40.8 ± 14.2 6015 | 36.3 ± 14.2 25634 | <0.001‡ |
| Weight (kg), age ≥ 18    | 83.2 ± 25.3 7238 | 81.3 ± 21.9 1318 | 83.7 ± 26.1 5727 | 0.002‡ |
| Female                   | 11154 (25) | 2094 (30) | 8408 (22) | <0.001 |
| Oral exposure            | 32992 (73) | 6846 (97) | 24746 (65) | <0.001 |

| Season at time of intoxication | Total* | Intentional | Unintentional | P-value† |
|-------------------------------|--------|-------------|---------------|----------|
| Spring                        | 11398 (25) | 1890 (27) | 9508 (25) | 0.01    |
| Summer                        | 11467 (25) | 1781 (25) | 9686 (25.5) | —       |
| Fall                          | 11240 (25) | 1749 (25) | 9491 (25) | —       |
| Winter                        | 10992 (25) | 1650 (23) | 9342 (24.5) | —       |

| Reported signs and symptoms | Total* | Intentional | Unintentional | P-value† |
|------------------------------|--------|-------------|---------------|----------|
| Headache                     | 1238 (3) | 150 (2) | 1088 (3) | <0.001 |
| Nausea                       | 2625 (6) | 490 (7) | 2135 (6) | <0.001 |
| Vomiting                     | 2437 (5) | 872 (12) | 1565 (4) | <0.001 |
| Abdominal pain               | 897 (2) | 308 (4) | 589 (2) | <0.001 |
| Seizure (single/multiple)    | 184 (<1) | 172 (2) | 12 (<1) | <0.001 |
| Seizure (status)             | 22 (<1) | 20 (<1) | 2 (<1) | <0.001 |
| Coma                         | 716 (2) | 679 (10) | 37 (<1) | <0.001 |
| Anion gap acidosis           | 2723 (6) | 2491 (35) | 232 (<1) | <0.001 |
| Kidney damage                | 1516 (3) | 1396 (20) | 120 (<1) | <0.001 |

| Therapies                    | Total* | Intentional | Unintentional | P-value† |
|------------------------------|--------|-------------|---------------|----------|
| Intravenous fluids           | 4179 (10) | 3243 (46) | 936 (3) | <0.001 |
| Ethanol                      | 524 (1) | 377 (5) | 147 (<1) | <0.001 |
| Fomepizole                   | 4859 (11) | 3858 (55) | 1001 (3) | <0.001 |
| Admitted to ICU              | 4193 (9) | 3593 (51) | 600 (2) | <0.001 |
| Intubation                   | 1210 (3) | 1143 (16) | 67 (<1) | <0.001 |
| Renal replacement therapy    | 2456 (5) | 2294 (32) | 162 (<1) | <0.001 |

| Outcomes                     | Total* | Intentional | Unintentional | P-value† |
|------------------------------|--------|-------------|---------------|----------|
| Death                        | 154 (<1) | 144 (2) | 10 (<1) | <0.001 |
| Major effect                 | 1672 (4) | 1541 (22) | 131 (<1) | <0.001 |
| Moderate effect              | 3560 (8) | 1654 (23) | 1906 (5) | <0.001 |
| Minor effect                 | 7379 (16) | 806 (11) | 6573 (17) | <0.001 |

Plus-minus values are mean (SD) and number of patients reporting
*Total is intentional plus unintentional ingestions
† P-Value compares intentional versus unintentional intoxication, Chi-square test unless otherwise noted, Bonferroni-corrected p-value for significance is <0.002 (0.05/28 comparison variables)
‡ P-value calculated using a Student’s unpaired two-tailed t-test

doi:10.1371/journal.pone.0143044.t001
gender (30% versus 22%, \( p < 0.001 \)), kidney damage (20% versus <1%, \( p < 0.001 \)), fomepizole use (55% versus 3%, \( p < 0.001 \)), and need for renal replacement therapy (32% versus <1%, \( p < 0.001 \)). Outcomes were also worse for the intentional exposure group, with a higher frequency of major effects (22% versus <1%, \( p < 0.001 \)) and death (2% versus <1%, \( p < 0.001 \)).

Effects and Outcomes of Individuals Exposed to Ethylene Glycol

We compared characteristics of exposed individuals based on clinical severity of exposure and found significant differences for all comparisons. Overall, 21,895 poisoned individuals were followed to three categories of known outcome: minor or no effects (N = 16,155), moderate effects (N = 3714), and major effects or death (N = 2026, groups compared in Table 2). Individuals who died or sustained major effects were older (44 years) compared to those with no or only minor effects (29.8 years), and more often male (72% versus 77%) and exposed intentionally (93% versus 13%).

### Table 2. Characteristics of Patients Who Experienced Effects Attributed to Ethylene Glycol Poisoning

| Characteristics                  | Minor and no effects | Moderate effects | Death and major effects |
|----------------------------------|----------------------|------------------|------------------------|
| Number of patients, N (%)        | 16155 (100)          | 3714 (100)       | 2026 (100)             |
| Age at intoxication\( ^\dagger \) | 29.8 ± 17.5 14421   | 37.8 ± 15.2 3476 | 44.0 ± 15.0 1983      |
| Age ≥ 18 at intoxication\( ^\ddagger \) | 36.3 ± 14.3 11135 | 39.3 ± 14.2 3275 | 44.9 ± 14.3 1929     |
| Weight (kg), age ≥ 18\( ^\ddagger \) | 82.0 ± 27.0 2994   | 80.9 ± 21.6 670  | 80.2 ± 21.9 424      |
| Female§                          | 3720 (23)            | 1003 (27)        | 576 (28)               |
| Oral exposure§                   | 11538 (71)           | 2383 (64)        | 1938 (96)              |
| Unintentional§                   | 14009 (87)           | 1910 (52)        | 144 (7)                |
| Unintentional, age < 18§         | 3149 (20)            | 140 (4)          | 49 (2)                 |

#### Reported signs and symptoms

|                     | Minor and no effects | Moderate effects | Death and major effects |
|---------------------|----------------------|------------------|------------------------|
| Headache            | 497 (3)              | 153 (4)          | 46 (2)                 |
| Nausea              | 1205 (8)             | 303 (8)          | 182 (9)                |
| Vomiting            | 1041 (6)             | 382 (10)         | 344 (17)               |
| Abdominal pain      | 396 (3)              | 153 (4)          | 95 (5)                 |
| Seizure (single/multiple) | 4 (<1)       | 16 (<1)          | 192 (10)               |
| Seizure (status)    | 0 (0)                | 2 (<1)           | 22 (1)                 |
| Coma                | 3 (<1)               | 123 (3)          | 664 (33)               |
| Anion gap acidosis  | 43 (<1)              | 1234 (33)        | 1614 (80)              |
| Kidney damage       | 14 (<1)              | 361 (10)         | 1246 (61)              |

#### Therapies

|                     | Minor and no effects | Moderate effects | Death and major effects |
|---------------------|----------------------|------------------|------------------------|
| Intravenous fluids  | 1268 (8)             | 1361 (37)        | 1452 (72)              |
| Ethanol             | 176 (1)              | 156 (4)          | 151 (8)                |
| Fomepizole          | 1517 (9)             | 1624 (44)        | 1614 (80)              |
| Admitted to ICU     | 918 (6)              | 1493 (40)        | 1712 (85)              |
| Intubation          | 16 (<1)              | 261 (7)          | 1007 (50)              |
| Renal replacement therapy | 164 (1)         | 847 (23)         | 1534 (76)              |

Plus-minus values are mean (SD) with number of patients reporting. Bonferroni-corrected \( p \)-value for significance is <0.002 (0.05/19 comparison variables).

* Includes all classifications of intention, see methods
\( ^\dagger \) \( p \)-value calculated using Chi-square, \( p < 0.001 \) for both age rows, compared by effects
\( ^\ddagger \) \( p \)-value calculated using Chi-square, \( p = 0.290 \) for weight, compared by effects
§ \( p \)-value calculated using ANOVA comparing three column effect variables is \( p < 0.0001 \) for all row, variables shown

doi:10.1371/journal.pone.0143044.t002
Corresponding to the definitions of a major effect from exposure, those in this group were more likely to suffer kidney damage (n = 1246, 61%), be admitted to the ICU (n = 1712, 85%), and undergo intubation (n = 1007, 50%) and renal replacement therapy (n = 1534, 76%). Analysis of therapeutic interventions between 2006 and 2013 revealed stable rates of intravenous fluid and fomepizole use, but a significant decrease in the requirement for renal replacement and ethanol therapies (S4A and S4B Fig). During this period, there was also a decrease in the number of deaths and major effects (S4C and S4D Fig).

Multivariable analysis revealed the following statistically significant predictors of intentional ethylene glycol exposure: age over 18 years, female gender, oral route of exposure, and spring compared to fall (Fig 1A, numerical data in S4 Table). Specifically with regards to gender, more men were exposed to ethylene glycol overall and more men intentionally ingested ethylene glycol; however, this analysis implies that women exposed to ethylene glycol are more likely to experience more serious effects. The risk of intentional ingestion for winter and summer fell between spring and fall and were not statistically distinct from either. Statistically significant predictors of major effect(s) and/or death were also identified: age 30 years and higher, spring compared to fall, and intentionality (Fig 1B). The risks of major effect(s) and/or death in winter and summer were similar to those in spring. These findings were identical when analyzing predictors of major effect(s) or death separately (data not shown). Model discrimination was strong in both models (intentional ingestion C-statistic = 0.74, major effect(s) and/or death C-statistic = 0.92).

Geographic Trends of Ethylene Glycol Exposures

Choropleth maps depicting frequency of ingestion by population density are shown in the United States and the District of Columbia and based on intentionality, major outcomes and deaths combined, and in the pediatric population (age <18) (Fig 2). We compared population density to the first four variables and the percent of population under the age of 18 for pediatric ingestions. There was a strong negative correlation between ethylene glycol exposures and population density by state for total, unintentional, and intentional ingestions. There was no correlation between population density and the incidence of major effects or death, or the frequency of unintentional ingestions in the pediatric population. We found no difference with regard to exposures by latitude. Alaska had the highest number of intentional and unintentional ingestions (S2 Table for rankings). Hawaii had the lowest number of intentional ingestions and Florida had the lowest number of unintentional ingestions.

Effect of the Aversive Additive Denatonium Benzoate on Oral Ethylene Glycol Ingestion

Seventeen states now require addition of the bittering agent, denatonium benzoate, to ethylene glycol preparations as a means to deter individuals from ethylene glycol ingestion (S3 Table). Limiting our analysis to include only oral exposures, we found no significant difference when examining intentional and pediatric ingestions by year (Fig 3A and 3B). We examined the effect of this additive on oral ethylene glycol ingestions in states requiring addition of denatonium benzoate, as compared to states not requiring its addition, and found no significant difference in the total number of ingestions (p = 0.39), unintentional ingestions (p = 0.84), or pediatric ingestions (p = 0.151) (Fig 3C, 3D and 3F). In fact, there was a significant increase in the number of intentional ingestions in states with an enacted law (p = 0.034) (Fig 3E). Furthermore, there were no significant differences in deaths or major effects (Fig 3G and 3H).
Discussion

This analysis of all reported ethylene glycol exposures within the United States over the past eight years reveals characteristics that differentiate individuals with intentional or unintentional exposures. Those who intentionally exposed themselves to ethylene glycol were more...
Fig 2. Incidence proportion of ethylene glycol exposures and population correlations. Choropleth maps show incidence proportion for ethylene glycol exposures for (A) all, (B) intentional, (C) unintentional, (D) major effects and death and (E) pediatric unintentional exposures (≤6 years old). Panels F-J show corresponding state incidence proportions correlated with population density (population per square mile) by state (F-H), panel J shows incidence of pediatric unintentional exposures correlated to percent of population of children under 18 years old by state. Incidence is per 100,000 humans, r = Pearson’s correlation coefficient.

doi:10.1371/journal.pone.0143044.g002
Fig 3. The effect of addition of bittering agent to ethylene glycol on frequency of oral ingestions in the United States and the District of Columbia. Panels A and B show incidence of intentional (> 11 years old) and pediatric unintentional oral ingestions (< 6 years old) per year for all states. In 2012, bitter ant was added to commercially sold antifreeze in the United States and the District of Columbia. Panels C-F show no reduction in total, unintentional, intentional (> 11 years old), or pediatric unintentional oral ingestions (< 6 years old) of ethylene glycol in states that have added bitter ant to ethylene glycol (n = 17) compared to those that have not (n = 34) from 2006–2013. Panels G and H show no reduction in death or major effects in states that have added bitter ant compared to those that have not from 2006–2013. Y-axis represents frequency per 100,000 (100 K) humans for all panels; error is SEM; p-values calculated using analysis of variance for panels A and B.

doi:10.1371/journal.pone.0143044.g003
likely to be older, male, and to have more severe signs and symptoms at presentation that required more intensive therapy. Although deaths and major effects were uncommon and have been decreasing since 2006 [31], individuals who died and/or experienced major effects, regardless of intent, have more severe signs and symptoms and were more likely to require aggressive care. Multivariable analysis confirmed older age and female gender as predictors of intentionality as well as oral route of exposure; that is, for all individuals exposed to ethylene glycol, women were more likely to have been exposed intentionally, and those who ingested ethylene glycol orally were more likely to have done so intentionally. Deaths, major effects, and moderate effects were also more common in this group. Significant predictors of major effects and death included older age and intentionality. As previously reported, we confirmed that fomepizole use has supplanted ethanol as an antidote for ethylene glycol poisoning. This finding corroborates prior studies showing the benefit of fomepizole over ethanol [7,10].

Contrary to our expectations, cases of ethylene glycol exposure were not associated with northerly latitude or season. Another unexpected finding not shown previously was the association of cases of intentional and/or unintentional exposures with low population density; that is, states with low population density had more reported exposures per capita. This pattern has not been seen in other types of poisonings in the United States; however, there are low population density associations with other types of injuries. For example, a retrospective study recently reported that Americans in rural regions were more likely to die from unintentional firearm injuries than those in urban regions [32]. Additionally, suicide rates of rural youth are nearly double those of urban youth [33]. States with lower population density may have a greater need for vehicular use, which would suggest increased exposure to ethylene glycol. Those who live in areas of low population density may be more likely to service their own vehicle. This suggests that resources aimed at decreasing exposures should be targeted to rural areas.

Limited data exist regarding characteristics of individuals exposed to ethylene glycol and predictors of poor outcomes [34]. Analysis of California data revealed an association of more severe clinical signs with individuals exposed to ethylene glycol between 1999 and 2008 who died or had prolonged renal insufficiency. Improved outcomes were seen with earlier antidote administration [35]. The degrees of osmolal and anion gaps have also been associated with increased mortality [2]. More recently, analysis of NPDS data between 2000 and 2013 revealed that fomepizole use has essentially replaced ethanol as a treatment modality and that the use of renal replacement therapy is trending down [31]. Our analysis confirms these findings on a national level and provides additional insight into the link between intention and case outcome.

Most importantly, we found no change in the number of oral ingestions in states that have required addition of denatonium benzoate to ethylene glycol preparations. In fact, the number of intentional exposures has significantly increased. This suggests that the addition of an aversive agent to ethylene glycol may not reduce harm to those who are most affected—individuals who attempt to commit suicide by ethylene glycol ingestion—as was previously shown in two states [24]. One of the first commercial uses of denatonium benzoate was as an aversive bittering agent in a Danish pig farming community where it was applied to pigs’ tails to avoid cannibalization [36]. Studies have shown that small concentrations of denatonium benzoate were effective in reducing the volume of material swallowed by children [37]; subsequent studies have supported this finding [38–40]. It is unclear if addition of denatonium benzoate would prevent or lessen ethylene glycol poisoning, given that small volumes of ethylene glycol are toxic; however, denatonium benzoate may be effective in reducing severity rather than frequency of exposure by reducing the volume ingested, which requires future investigation. One could hypothesize that individuals who intentionally ingest ethylene glycol may be more likely
to ingest large quantities regardless of bitterness given the intention to inflict self-harm. Single
state studies reinforce our conclusions by demonstrating that addition of denatonium benzoate
to ethylene glycol in Oregon and California did not affect rates of ethylene glycol poisoning in
animals and humans [22–24]. These findings differ from those seen with legislation to prevent
other types of fatalities. For example, more firearm laws are associated with fewer firearm-
related fatalities in the United States [41].

One limitation of this study relates to NPDS data in general [42]. Case records reflect infor-
mation provided when the public or healthcare professionals report an actual or potential
exposure to a substance. Exposures do not necessarily represent a poisoning or overdose [43].
The AAPCC is not able to verify the accuracy of every report made to centers. There is also het-
erogeneity of coding practices across poison centers. Certain infrequent clinical effects are
potentially coded less often than those with greater familiarity, but efforts were made to limit
under-coding by combining related clinical effects to capture more severe effects. This con-
founder is likely similar across all centers and therefore, would not affect conclusions drawn
here. Case outcomes can also be erroneously up-coded in severity, which could potentially
result in greater reported severity of all cases, but comparison between intention and state inci-
dance across time should not be affected. In addition, some fatalities could have been missed in
individuals who died outside of a medical setting. Future efforts to identify such individuals are
needed and could include analysis of state medical examiner death records. Additionally, pro-
spective and longitudinal collection of clinical data from patients with ethylene glycol poison-
ing across major medical centers is warranted to validate and increase granularity of findings
presented here.

Since its discovery by Charles-Adolphe Wurtz in 1856 [44], ethylene glycol has become a
major commercial commodity. The ethylene glycol industry exceeds $21 billion in annual mar-
ket value [45], and demand is increasing. In 2013, 86% of worldwide consumption of mono-
ethylene glycol went into the production of polyethylene terephthalate (PET) (fibers, film and
bottles), and 7.5% was used to produce antifreeze [46]. Alternative means to deter intentional
and unintentional consumption are needed. For example, improved labeling and mandatory
use of child-proof caps are effective in deterring consumption of toxic agents, at least in chil-
dren [47]. Our findings suggest replacing ethylene glycol as a main component in antifreeze
with alternative and less toxic agents with similar properties, such as propylene glycol or gly-
cerol [48], as the morbidity associated with this product is significant, approved alternatives
exist, and deterrents are, in our analysis, ineffective. This study is the first to provide an in-
depth analysis of demographic, clinical, and therapeutic data related to trends in ethylene gly-
col exposures in the United States, and suggests the need to identify and implement more effec-
tive preventative strategies to reduce ethylene glycol poisoning.

Supporting Information
S1 Fig. Determination of weight of all ethylene glycol-exposed individuals under two years
of age. Weight values for children under two years of age were validated to correct for unit
errors (pounds instead of kilograms) that occurred during data entry. This was performed by
visualizing weight of all patients under two years of age and comparing the values to 150% of
the normal values by age (WHO growth charts for reference). Panel A shows two lines fit to
the data using growth chart data. Panel B shows the data after the outliers were divided by
2.205 to convert pounds to kilograms with the assumption that outliers were incorrectly
entered in pounds instead of kilograms.

(TIF)
S2 Fig. Flow chart of study subject selection.

S3 Fig. Incidents of ethylene glycol exposures from 2006–2013. Number of intentional, unintentional and other (defined as “malicious,” “contamination,” “tampering,” “adverse reaction,” and “unknown”) exposures in the United States and District of Columbia plotted by year. There were no statistically significant differences across the inclusion period.

S4 Fig. Trends in therapies and outcomes after ethylene glycol exposure. Panels A and B show trends in use of therapies. Use of intravenous fluid and fomepizole have remained constant while use of renal replacement therapy and ethanol has declined. Panels C and D show trends in deaths and major effects. X-axis is years and Y-axis is number of times therapy or outcome was reported in year x per cases reported in year x.

S1 Table. Poison Control Centers within the United States Poison Control Network.

S2 Table. Rank of Top 20 States Based on Number of Intentional or Unintentional Ingestions during the Study Period.

S3 Table. Years that States Required Addition of Denatonium Benzoate to Ethylene Glycol Based Antifreeze Formulations.

S4 Table. Statistics from Logistic Regression Analysis of Risk Factors Associated with Ethylene Glycol Ingestion (Fig 1).

S5 Table. Reported Reason of Exposure to Ethylene Glycol.

Acknowledgments

The authors wish to thank the American Association of Poison Control Centers for access to the National Poison Data System, and the United States Poison Control Network for decades of case contributions. We would also like to thank Philip McDaniel, a Geographic Information Systems (GIS) services librarian at the University of North Carolina at Chapel Hill, who assisted with the use of ArcGIS and generation of choropleths.

WFP3 would like to thank the late Dr. Nate Hellman for founding the Renal Fellow Network (www.renalfellow.blogspot.com) and inspiring him through this venue to further investigate clinical effects of elevated anion gap metabolic acidoses.

Author Contributions

Conceived and designed the experiments: MAJ WFP MCB. Analyzed the data: MAJ SLH CSM YH GAH RJF MCB WFP. Contributed reagents/materials/analysis tools: MCB. Wrote the paper: MAJ WFP.
References

1. Cavender FL, Sowinski EJ. Patty's industrial hygiene and toxicology. 4 ed. Clayton G, Clayton F, editors. New York: John Wiley & Sons, Inc; 1994. pp. 4645–4657.

2. Coulter CV, Farquhar SE, McSherry CM, Isbister GK, Duffull SB. Methanol and ethylene glycol acute poisonings—predictors of mortality. Clinical Toxicology. 2011; 49: 900–906. doi: 10.3109/15563650.2011.630320 PMID: 22091788

3. Bronstein AC, Spyker DA, Cantilena LR Jr, Rumack BH, Dart RC. 2011 Annual Report of the American Association of Poison Control Centers’ National Poison Data System (NPDS): 29th Annual Report. Clinical Toxicology. 2012; 50: 911–1164. doi: 10.3109/15563650.2012.746424

4. Wax PM, Elixirs, diluents, and the passage of the 1938 Federal Food, Drug and Cosmetic Act. Ann Intern Med. 1995; 122: 456–461. PMID: 7856995

5. Alkahtani S, Sammons H, Choonara I. Epidemics of acute renal failure in children (diethylene glycol toxicity). Arch Dis Child. 2010; 95: 1062–1064. doi: 10.1136/adc.2010.183392 PMID: 21062849

6. Haggerty RJ. Toxic hazards. Deaths from permanent antifreeze ingestion. N Engl J Med. 1959; 261: 1296–1297. doi: 10.1056/NEJM195912172612514 PMID: 15403194

7. Brent J. Current management of ethylene glycol poisoning. Drugs. 2001; 61: 979–988. PMID: 11434452

8. Berman LB, Schreiner GE, Feys J. The nephrotoxic lesion of ethylene glycol. Ann Intern Med. 1957; 46: 611–619. PMID: 13403542

9. Kahn HS, Brotchner RJ. A recovery from ethylene glycol (anti-freeze) intoxication; a case of survival and two fatalities from ethylene glycol including autopsy findings. Ann Intern Med. 1950; 32: 284–294. PMID: 15403194

10. Brent J. Fomepizole for ethylene glycol and methanol poisoning. N Engl J Med. 2009; 360: 2216–2223. doi: 10.1056/NEJMct0806112 PMID: 19458366

11. Brent J, McMartin K, Phillips S, Burkhart KK, Donovan JW, Wells M, et al. Fomepizole for the treatment of ethylene glycol poisoning. Medicalprazole for Toxic Alcohols Study Group. N Engl J Med. 1999; 340: 832–838. doi: 10.1056/NEJM1999031834001102 PMID: 10080845

12. Baud FJ, Galliot M, Astier A, Bien DV, Garnier R, Likforman J, et al. Treatment of ethylene glycol poisoning with intravenous 4-methylpyrazole. N Engl J Med. 1988; 319: 97–100. doi: 10.1056/NEJM198807143190206 PMID: 3380132

13. Caravati EM, Erdman AR, Christianson G, Manoguerra AS, Booze LL, Woolf AD, et al. Ethylene glycol exposure: an evidence-based consensus guideline for out-of-hospital management. Clinical Toxicology (Philadelphia, Pa.). 2005. pp. 327–345.

14. Peterson CD, Collins AJ, Himes JM, Bullock ML, Keane WF. Ethylene glycol poisoning: pharmacokinetics during therapy with ethanol and hemodialysis. N Engl J Med. 1981; 304: 21–23. doi: 10.1056/NEJM198101013040105 PMID: 7432434

15. Wacker WEC. Treatment of ethylene glycol poisoning with ethyl alcohol. JAMA. 1965; 194: 1231. doi: 10.1001/jama.1965.03090240065018 PMID: 5897748

16. Guinness World Records 2013. Guinness World Records; 2012.

17. British Columbia Regulation 142/2009. Antifreeze regulation in the Environmental Management Act. British Columbia, 2009.

18. Oregon Revised Statute 431.880. Aversive agent required. State of Oregon, 1991.

19. Oregon Revised Statute 431.885. Toxic household products required to comply with aversive agent requirement; exemptions. State of Oregon, 1991.

20. U.S. Senate. 109th Congress, First session. S. 1110, the engine coolant and antifreeze bittering agent act of 2005: hearing before the Subcommittee on Consumer Affairs, Product Safety. Washington: Government Printing Office, 2005.

21. Consumer Safety Product Association. Making antifreeze and engine coolant unpalatable to humans and animals. Available: http://www.cspa.org/advocacy/our-issues/129.html, Accessed June 13, 2014.

22. Mullins ME, Zane Horowitz B. Was it necessary to add Bitrex (denatonium benzoate) to automotive products? Vet Hum Toxicol. 2004; 46: 150–152. PMID: 15171494

23. White NC, Litovitz T, Benson BE, Horowitz BZ, Marr-Lyon L, White MK. The Impact of Bittering Agents on Pediatric Ingestions of Antifreeze. Clin Pediatr (Phila). 2009; 48: 913–921. doi: 10.1177/0009922809393522

24. White NC, Litovitz T, White MK, Watson WA, Benson BE, Horowitz BZ, et al. The impact of bittering agents on suicidal ingestions of antifreeze. Clinical Toxicology. 2008; 46: 507–514. doi: 10.1080/15563650802119700 PMID: 18584362
25. WHO child growth standards: growth velocity based on weight, length and head circumference methods and development. World Health Organization; 2009.

26. Beuher MC, Wittler MA, Ford M, Dulaney AR. A controlled evaluation of case clinical effect coding by poison center specialists for detection of WMD scenarios. Clinical Toxicology. 2011; 49: 684–690. doi: 10.3109/15563650.2011.598530 PMID: 21819293

27. Sasser H, Nussbaum M, Beuher M, Ford M. Classification tree methods for development of decision rules for botulism and cyanide poisoning. J Med Toxicol. 2008; 4: 77–83. PMID: 18570166

28. Wickham H. The split-apply-combine strategy for data analysis. Journal of Statistical Software. 2011;

29. Synder JP. Map projections: a working manual. Washington, DC: U.S. Department of the Interior, U.S. Geological Survey; 2011 Nov pp. 1–397. Report No.: 1395.

30. Minnesota Population Center. National Historical Geographic Information System: Version 2.0. Minneapolis, MN: University of Minnesota 2011. Available: http://www.nhgis.org.

31. Ghannoum M, Hoffman RS, Mowry JB, Lavergne V. Trends in toxic alcohol exposures in the United States from 2000 to 2013: a focus on the use of antidotes and extracorporeal treatments. Semin Dial. 2014; 27: 1–7.

32. Carr BG, Nance ML, Branas CC, Wolff CS, Kallan MJ, Myers SR, et al. Unintentional firearm death across the urban-rural landscape in the United States. J Trauma Acute Care Surg. 2012; 73: 1006–1010. PMID: 22976424

33. Porter WH, Rutter PW, Bush BA, Pappas AA, Dunnington JE. Ethylene glycol toxicity: the role of serum glycolic acid in hemodialysis. J Toxicol Clin Toxicol. 2001; 39: 607–615. PMID: 11762669

34. Finnell LF, DuBose Z, Shulman A, Weismiller D, Noonan M, Roberts P, et al. Trends in pediatric exposures to bromacil, an insecticide commonly used in the United States. Environ Health Perspect. 2003; 112: 157–162. doi: 10.1289/ehp.6021

35. Klein-Schwartz W. Denatonium benzoate: review of efficacy and safety. Vet Hum Toxicol. 1991; 33: 545–547. PMID: 1808826

36. Bitrex history. Available: http://www.bitrex.com/en-us/about-bitrex/history. Accessed 21 May 2014.

37. Berning CK, Griffin JL, Wild J. Research on the effectiveness of denatonium benzoate as a deterrent to liquid detergent ingestion by children. Fundamental and Applied Toxicology. 1982; 2: 44–48. doi: 10.1016/S0272-0590(82)80063-8 PMID: 7185601

38. Klein-Schwartz W. Denatonium benzoate: review of efficacy and safety. Vet Hum Toxicol. 1991; 33: 545–547. PMID: 1808826

39. Sibert JR, Frude N. Bittering agents in the prevention of accidental poisoning: children's reactions to denatonium benzoate (Bitrex). Arch Emerg Med. 1991; 8: 1–7. PMID: 1854387

40. Jackson MH, Payne HA. Bittering agents: their potential application in reducing ingestions of engine coolants and windshield wash. Vet Hum Toxicol. 1995; 37: 323–326. PMID: 8540219

41. Fleegler EW, Lee KK, Monuteaux MC, Hemenway D, Mannix R. Firearm legislation and firearm-related fatalities in the United States. JAMA Intern Med. 2013; 173: 732–740. doi: 10.1001/jamaientermmed.2013.1286 PMID: 23467753

42. Hoffman RS. Understanding the limitations of retrospective analyses of poison center data. Clin Toxicol (Phila). 2007; 45: 943–945. doi: 10.1080/15563650701233370

43. Lévy A, Bailey B, Letarte A, Dupuis C, Lefebvre M. Unproven ingestion: an unrecognized bias in toxicological case series. Clin Toxicol (Phila). 2007; 45: 946–949. doi: 10.1080/15563650701197096

44. Wurtz C-A. Sur le glycol ou alcool diatomique. Comptes Rendus. 1856; 43: 199–204.

45. Prospects look good for global ethylene oxide, ethylene glycol markets. In: Processing Magazine: Solutions for the Process Industry. 8 Aug 2013.

46. Chinn H, Kumamoto T. Mono-, Di-, and Triethylene Glycols. IHS Report; 2013 Nov. Report No.: http://chemical.ihs.com/CEH/Public/Reports/652.4000.

47. Sibert JR, Craft AW, Jackson RH. Child-resistant packaging and accidental child poisoning. Lancet. 1977; 35: 289–290.

48. Hudgens RD, Hencamp RD, Francis J, Nyman DA, Bartoli Y. An evaluation of glycerin (glycerol) as a heavy duty engine antifreeze/coolant base. Warrendale, PA: SAE International; 2007 Oct pp. 2007–01–4000. doi: 10.4271/2007-01-4000