J. Med. Toxicol. (2017) 13:203–226
DOI 10.1007/s13181-017-0627-3

ORIGINAL ARTICLE

The Toxicology Investigators Consortium Case Registry—the 2016 Experience

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Received: 30 June 2017 / Revised: 17 July 2017 / Accepted: 18 July 2017 / Published online: 1 August 2017

Abstract The Toxicology Investigators Consortium (ToxIC) Case Registry was established by the American College of Medical Toxicology in 2010. The Registry contains data from participating sites with the agreement that all bedside medical toxicology consultations will be entered. Currently, 83% of accredited medical toxicology fellowship programs in the USA participate. The Registry continues to grow each year, and as of 31 December 2016, a new milestone was reached, with more than 50,000 cases reported since its inception. The objective of this seventh annual report is to summarize the Registry's 2016 data and activity with its additional 8529 cases. Cases were identified for inclusion in this report by a query of the ToxIC database for any case entered from 1 January to 31 December 2016. Detailed data was collected from these cases and aggregated to provide information which includes the following: demographics (age, gender, race, ethnicity, HIV status), reason for medical toxicology evaluation (intentional pharmaceutical exposure, envenomation, withdrawal from a substance), agent and agent class, clinical signs and symptoms (vital sign abnormalities, organ system dysfunction), treatments and antidotes administered, fatality and life support withdrawal data. Fifty percent of cases involved females, and adults aged 19–65 were the most commonly reported. There were 86 patients (1.0%) with HIV-positive status known. Non-opioid analgesics were the most commonly reported agent class, with acetaminophen the most common agent reported. There were 126 fatalities reported in 2016 (1.5% of cases). Major trends in demographics and exposure characteristics remained similar overall with past years' reports. While treatment interventions were commonly required, fatalities were rare.

Keywords Poisonings · Overdose · Epidemiology · Medical toxicology

Electronic supplementary material The online version of this article (doi:10.1007/s13181-017-0627-3) contains supplementary material, which is available to authorized users.

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Introduction

The Toxicology Investigators Consortium (ToxIC) was created by the American College of Medical Toxicology (ACMT) in 2010 as a tool for clinical toxicology research and toxicosurveillance [1]. Unlike other poisoning databases, ToxIC is a prospective case registry based on medical toxicologists' experience performing consultations in both inpatient and ambulatory settings. Cases where a formal consultation was not done, such as where advice was given over the telephone, are not included in the database.

The ToxIC Registry is unique in several important ways. Because all information was entered by treating medical toxicologists, the toxicological data reflects the best professional judgment of skilled clinicians. Much of the information on the database is not available from other sources and includes not only medical data but also demographics including race and ethnicity and HIV status.

In 2016, there was a 2.0% decrease in sites included in the ToxIC Registry, with four sites added and five withdrawn or dropped from participation because they withdrew or failed to meet quality standards set by the Registry. Two of the international sites were not included in 2016 due to withdrawal or lack of case entry. At the end of 2016, there were 46 sites, comprising 79 facilities with active case entry. Currently, 83% of active accredited medical toxicology fellowship programs in the USA participate in the ToxIC Registry. The objective of this report is to summarize the Registry's 2016 data and activity. Cases entered in 2016 are described in this seventh annual report.

Since its inception, several supplemental or subregistries have been created within ToxIC. These are designed to collect more detailed information in specific areas. Our subregistries studying caustic ingestions and prescription opioid abuse were closed at the end of 2016; data from these subregistries are now being analyzed. Subregistries on lipid resuscitation therapy, North American snake bites, and extracorporeal substance removal continued to collect data in 2016 and are continuing into 2017. Three additional subregistries were approved and developed in 2016 and became live on January 1, 2017; these include subregistries on plant, mushroom and herbal toxicity; pediatric opioid exposures; and pediatric marijuana exposures.

In 2016, 14 abstracts and five manuscripts using ToxIC Registry data were published and are listed on http://www.ToxICRegistry.org (Farrugia et al. [2]; Beauchamp et al. [3]; Judge et al. [4]; Riederer et al. [5]; Wang et al. [6]).

In 2016, ToxIC was supported by a continuation of a grant from the US National Institutes of Health on cardiovascular drug toxicity, a new contract with the US Food and Drug Administration, and the continuation of unrestricted grant support from BTG International, which was used to support the North American Snakebite Registry.

Methods

A detailed description of the creation and design of the ToxIC Registry has been previously reported by Wax et al. [1]. To be part of the consortium, all medical toxicologists at participating institutions agree to enter data into the ToxIC Registry on all medical toxicology consultations performed. Cases are entered on a password-protected encrypted online data collection form. The site is maintained by ACMT with oversight by the ToxIC Leadership Group. The Registry is compliant with the Health Insurance Portability and Accountability Act (HIPAA) and does not collect any protected health information or otherwise identifying fields. Registry participation is pursuant to the participating institution's Institutional Review Board (IRB) approval and compliant with their policies and procedures. The Registry has also been independently reviewed by the Western IRB and determined not to meet the threshold of human subject research under federal regulation 45 CFR 46 and associated guidance.

Data collected on each case include presenting signs and symptoms, clinical course, treatments, limited patient demographics, outcome, laboratory values, and circumstances of and reasons for toxicological exposure. The term "consultation" is used in this report to describe any in-person encounter with a medical toxicologist in which a formal evaluation was conducted and placed in the medical record. Such encounters may include admission to a medical toxicology in-patient service, or evaluation by a medical toxicologist as a consulting physician in an emergency department, inpatient unit, or outpatient clinic. The online data collection form is formatted to ensure data entry remains organized and searchable. Free text entry fields allow providers to provide further detail or supplementary information. As part of the Registry's toxicosurveillance mission, one component of the standard data form is a sentinel detection field that signals novel or unusual cases. Analysis of novel exposure surveillance data in the Registry has begun, with results to be published in a separate report.

For this report, a search of the database was performed to identify cases recorded from January 1, 2016, through December 31, 2016. Additional data from the subregistries will be published separately. This descriptive report summarizes case demographics, source and location of consultation, and reasons for encounter, and provides case frequencies by individual agent class and treatment provided.

In the tables describing individual agents or agent classes, unless otherwise indicated, values with fewer than five occurrences were not listed as separate items but are further grouped as "miscellaneous." Percentages noted in tables for individual agents represent their relative proportion within their respective agent class.

For clinical signs or symptoms, the tables provide the percentage of individual signs or symptoms relative to the total

number of Registry cases in 2016. Signs and symptoms include the presence or absence of a toxidrome, vital sign abnormalities, and a variety of organ system-based derangements which may arise from a toxic exposure. For each subheading in the data collection instrument, investigators are required to either select an abnormality, or "None," to improve the accuracy of data collection. In the detailed treatment tables, percentages for each treatment modality represent the relative frequency among all treatments rendered.

Results

A total of 8529 cases were entered in the ToxIC Registry in 2016, up slightly from 8115 in 2015 (Fig. 1) [2]. Table 1 lists the individual sites entering cases in 2016.

Demographics

Selected demographics are summarized in Tables 2, 3, 4, 5, 6, 7, and 8. In 2016, male (50.0%) and female (50.0%) cases were distributed evenly and 0.6% were pregnant. Adults age 19–65 years comprised the majority (67.0%) of cases, with children age 13–18 years the next most common (16.8%). There were a total of 2280 (26.7%) pediatric cases (0–18 years) overall. The most commonly reported race categories were Caucasian (58.1%) and black/African (14.1%), with 18.0% unknown/uncertain. Nine hundred fifty-one cases (11.2%) reported Hispanic ethnicity, while 19.1% reported ethnicity as unknown. Race and ethnicity are not self-reported in the Registry, and limitations in these data points continue to be addressed with ongoing quality improvement measures.

Table 4 presents demographic data on the 86 HIV-positive patients (1.0%) reported in the Registry. Table 5 details the referral source of medical toxicology evaluations. Table 6 provides information on the type of exposure which prompted a medical toxicology encounter. More detailed information on the intent surrounding the intentional pharmaceutical exposures is provided in Table 7. Table 8 depicts the frequency of common types of exposures as broken down by race, ethnicity, and gender. In all races, and for both Hispanics, non-Hispanics, and both genders, intentional pharmaceutical exposures were more common than intentional non-pharmaceutical exposures.

Agent Classes

There were 11,352 individual agent entries in 2016 for 8529 reported cases with 2519 (29.5%) cases involving multiple agents. The top agent classes were the same as 2015 [2], with non-opioid analgesics the most common (12.8%), followed by sedative-hypnotics/muscle relaxants (11.8%), antidepressants (11.1%), and opioids (9.8%) (Table 9).

Individual Agents by Class

Tables 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, and 26 show frequencies of individual agent entries by class, presented in order of most to least common class. Three agents—ethanol, lithium, and amphetamine-like hallucinogens—are their own classes but are reported with other agent classes (toxic alcohols, anticonvulsants and mood stabilizers, and psychoactives, respectively) for brevity. Tables S1–S18 in the Supplementary Material present frequencies for agent classes with little diversity, few overall cases, or when infrequently reported miscellaneous agents made up a significant portion of entries.

Table 10 presents the non-opioid analgesics class. This has been the most frequently reported agent class since 2013 [2, 7, 8]. The most common agent was acetaminophen (67.9%),

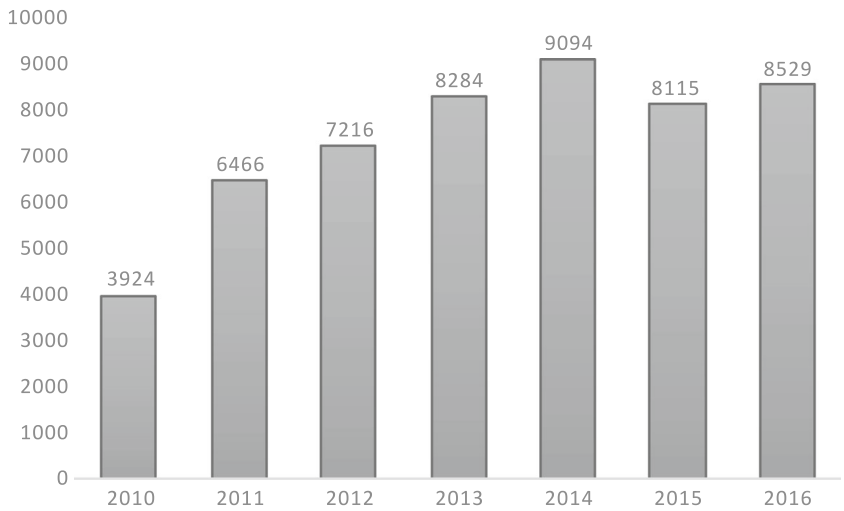

Fig. 1 Case numbers

Table 1 Participating institutions providing cases to ToxIC in 2016

- Arizona
  - Phoenix
    - Banner- University Medical Center Phoenix
    - Phoenix Children's Hospital
- California
  - Fresno
    - UCSF Fresno Medical Center
  - Loma Linda
    - Loma Linda University Medical Center
  - Los Angeles
    - University of Southern California Verdugo Hills
  - San Diego
    - Rady Children's Hospital
  - San Francisco
    - San Francisco General Hospital
- Colorado
  - Denver
    - Children's Hospital Colorado
    - Denver Health Medical Center
    - Porter and Littleton Adventist Hospital
    - Swedish Medical Center
    - University of Colorado Medical Center
- Connecticut
  - Hartford
    - Hartford Hospital
- Georgia
  - Atlanta
    - Children's Healthcare of Atlanta Egelston
    - Children's Healthcare of Atlanta Hughes Spalding
    - Emory University Hospital
    - Emory University Hospital Midtown
    - Grady Health System
    - Grady Memorial Hospital
- Illinois
  - Chicago
    - Cook County Hospital
  - Evanston
    - Evanston North Shore University Health System
- Indiana
  - Indianapolis
    - IU-Eskenazi Hospital
    - IU-Indiana University Hospital
    - IU-Methodist Hospital-Indianapolis
    - IU-Riley Hospital for Children
    - IU Wishard Memorial Hospital
- Massachusetts
  - Boston
    - Beth Israel Boston
    - Children's Hospital Boston
  - Worcester
    - University of Massachusetts Memorial Medical Center
- Michigan
  - Grand Rapids
    - Spectrum Health Hospitals
- Minnesota
  - St. Paul
    - Regions Hospital
- Missouri
  - Kansas City
    - Children's Mercy Hospitals & Clinics
  - St. Louis
    - Washington University School of Medicine
- Nebraska
  - Omaha
    - University of Nebraska Medical Center
- New Mexico
  - Albuquerque
    - University of New Mexico
- New Jersey
  - Morristown
    - Morristown Medical Center
  - New Brunswick
    - Robert Wood Johnson University Hospital
  - Newark
    - NJMS/Rutgers
- New York
  - Albany
    - Albany Medical Center
  - Manhasset
    - Long Island Jewish
    - North Shore University Hospital
  - New York
    - Bellevue Medical Center
    - Mount Sinai Hospital
    - NYU Langone Medical Center
  - Staten Island
    - Staten Island University Hospital
  - Rochester
    - Highland Hospital
    - Strong Memorial Hospital
  - Syracuse
    - Upstate Medical University-Downtown Campus
- North Carolina
  - Charlotte
    - Carolinas Medical Center
  - Greenville
    - Vidant Medical Center
- Oregon
  - Portland
    - Doernbecher Children's Hospital
    - Oregon Health & Science University Hospital
- Pennsylvania
  - Harrisburg
    - PinnacleHealth-Community General Osteopathic
    - PinnacleHealth-Harrisburg Hospital
    - PinnacleHealth-West Shore
  - Lehigh Valley
    - Lehigh Valley Hospital Cedar Crest
    - Lehigh Valley Hospital Muhlenberg
  - Philadelphia
    - Hahnemann University Hospital
    - Mercy Fitzgerald Hospital
    - Mercy Hospital of Philadelphia
    - St. Christopher's Hospital for Children

Table 1 (continued)

Pittsburgh
UPMC Children's Hospital of Pittsburgh
UPMC Magee Women's Hospital
UPMC Mercy Hospital
UPMC Presbyterian/Shadyside
Texas
Dallas
Children's Medical Center Dallas
Parkland Memorial Hospital
University of Texas Southwestern Clinic
William P Clements University Hospital
Houston
Ben Taub General Hospital
Texas Children's Hospital
San Antonio
San Antonio Military Medical Center
Utah
Salt Lake City
Primary Children's Hospital
University of Utah Hospital
Virginia
Charlottesville
University of Virginia Health Systems
Richmond
Virginia Commonwealth University Medical Center
Wisconsin
Milwaukee
Froedtert Memorial Lutheran Hospital
Israel
Haifa
Rambam Health Care Campus

which was also the most common agent in the Registry overall, involved in 11.6% cases, consistent with previous years.

Table 11 reports the sedative-hypnotics/muscle relaxants class. Benzodiazepines were the most frequently reported (52.6%) with alprazolam (20.6%), clonazepam (15.5%), and lorazepam (7.4%) the top three reported. In 2016, alprazolam eclipsed clonazepam as the most commonly reported

Table 2 ToxIC 2016 case demographics—age and gender

	N (%)
Gender	
Male	4267 (50.0)
Female	4262 (50.0)
Pregnant	47 (0.6)
Age (years)	
<2	270 (3.2)
2–6	358 (4.2)
7–12	215 (2.5)
13–18	1437 (16.8)
19–65	5714 (67.0)
66–89	477 (5.6)
>89	21 (0.2)
Unknown	29 (0.4)
Total	8529 (100)

Table 3 ToxIC 2016 case demographics—race and Hispanic ethnicity

	N (%)
Race	
Caucasian	4953 (58.1)
Unknown/uncertain	1537 (18.0)
Black/African	1201 (14.1)
Other	466 (5.5)
Asian	169 (2.0)
American Indian/Alaska Native	76 (0.9)
Mixed	108 (1.3)
Native Hawaiian or Pacific Islander	18 (0.2)
Australian aboriginal	1 (0.0)
Total	8529 (100)
Hispanic ethnicity[a]	
Hispanic	951 (11.2)
Non-Hispanic	5949 (69.8)
Unknown	1629 (19.1)
Total	8529 (100)

[a] Hispanic ethnicity as indicated exclusive of race

Table 4 ToxIC 2016 case demographics—HIV-positive patients

	N (%)
Reason for encounter	
Intentional pharmaceutical	42 (49.0)
Attempt at self-harm	27 (31.4)
Misuse/abuse	8 (9.3)
Therapeutic use	3 (3.5)
Unknown	4 (4.7)
Intentional non-pharmaceutical	24 (28.0)
Attempt at self-harm	1 (1.1)
Misuse/abuse	19 (22.1)
Unknown	3 (3.5)
Use for therapeutic intent	1 (1.1)
Unintentional pharmaceutical	1 (1.1)
Unintentional non-pharmaceutical	4 (5.0)
Race	
American Indian/Alaskan Native	1 (1.1)
Black/African	29 (33.7)
Caucasian	36 (42.0)
Other	9 (10.5)
Unknown/uncertain	11 (12.8)
Ethnicity	
Hispanic	10 (11.6)
Not Hispanic	62 (72.1)
Unknown	14 (16.3)
Total HIV-positive patients	86 (100)

Table 5 ToxIC 2016 case referral sources by inpatient/outpatient status

	N (%)
Emergency department (ED) or inpatient (IP)[a]	
ED	4772 (59.8)
Admitting service	2085 (26.1)
Outside hospital transfer	729 (9.1)
Request from another hospital service (not ED)	362 (4.5)
Poison Center	27 (0.3)
Primary care provider or other outpatient treating physician	5 (0.1)
Self-referral	5 (0.1)
ED/IP total	7985 (100)
Outpatient (OP)/clinic/office consultation[b]	
Primary care provider or other OP physician	231 (42.5)
Self-referral	211 (38.8)
Poison Center	42 (7.7)
Employer/independent medical eval	39 (7.2)
ED	15 (2.8)
Admitting service	3 (0.6)
Request from another hospital service (not ED)	3 (0.6)
OP total	544 (100)

[a] Percentage based on the total number of cases (*N* = 7985) seen by a medical toxicologist as consultant (ED or IP) or as attending (IP)

[b] Percentage based on the total number of cases (*N* = 544) seen by a medical toxicologist as outpatient, clinic visit, or office consultation

Table 6 ToxIC 2016 cases—primary reason for medical toxicology encounter

	N (%)
Intentional exposure—pharmaceutical	4591 (53.8)
Intentional exposure—non-pharmaceutical	1038 (12.2)
Unintentional exposure—pharmaceutical	659 (7.7)
Organ system dysfunction	309 (3.6)
Unintentional exposure—non-pharmaceutical	296 (3.5)
Envenomation—snake	285 (3.3)
Unknown	275 (3.2)
Withdrawal—opioid	264 (3.1)
Interpretation of toxicology data	177 (2.1)
Environmental evaluation	149 (1.7)
Withdrawal—ethanol	140 (1.6)
Occupational evaluation	121 (1.4)
Ethanol abuse	90 (1.1)
Envenomation—spider	43 (0.5)
Withdrawal—sedative/hypnotic	27 (0.3)
Malicious/criminal	22 (0.3)
Withdrawal—other	13 (0.2)
Envenomation—other	10 (0.1)
Envenomation—scorpion	7 (0.1)
Marine/fish poisoning	7 (0.1)
Withdrawal—cocaine/amphetamine	6 (0.1)
Total	8529 (100)

benzodiazepine for the first time since the ToxIC Registry began [2, 7–11]. Other commonly reported agents in this class included the muscle relaxants cyclobenzaprine and baclofen, gabapentin (in the "Other sedatives" subclass), and zolpidem (in the "Non-benzodiazepine agonists" subclass). Barbiturates were infrequently mentioned, consistent with prior years.

Table 12 presents the antidepressant class. Bupropion (in the "Other antidepressants" subclass) was the most frequently reported, comprising 20.7% of antidepressant cases and 3.0% of 2016 Registry cases overall, consistent with prior years. The selective serotonin reuptake inhibitors (SSRIs), particularly sertraline and fluoxetine, were the second most common subclass (34.3%), followed by the tricyclic antidepressants (TCAs) (15.1%) (e.g., amitriptyline), and the serotonin-norepinephrine reuptake inhibitors (SNRIs) (e.g., venlafaxine).

Table 13 summarizes opioid frequencies, including naturally derived, synthetic, and semisynthetic agents. As in previous years, heroin was the most commonly reported (28.3%), followed by oxycodone (17.8%) and methadone (8.9%).

Table 14 reports the sympathomimetic class. Cocaine was the most commonly reported (34.3%), followed by methamphetamine (25.7%) and amphetamine (12.4%), consistent with previous years. The pharmaceutical stimulants methylphenidate and lisdexamfetamine together accounted for 9.9% of the class. A number of designer stimulant drugs were reported, with methylenedioxy-N-methamphetamine the most common (4.3%). Less common designer agents, combined

Table 7 ToxIC 2016 cases—detailed reason for encounter, intentional pharmaceutical exposures

	N (%)
Reason for intentional pharmaceutical exposure subgroup[a]	
Attempt at self-harm	3099 (67.5)
Misuse/abuse	915 (19.9)
Therapeutic use	376 (8.2)
Unknown	202 (4.4)
Total	4592 (100)
Attempt at self-harm—suicidal intent subclassification[b]	
Suicidal intent	2700 (87.1)
No suicidal intent	115 (3.7)
Suicidal intent unknown	284 (9.2)
Total	3099 (100)

[a] Percentage of total number of cases (*N* = 4592) indicating primary reason for encounter due to intentional pharmaceutical exposure

[b] Percentage of number of cases (*N* = 3099) indicating attempt at self-harm

Table 8 ToxIC 2016 case demographics—race/gender/ethnicity and exposure type

	Intentional pharmaceutical, *N* (%)	Intentional non-pharmaceutical, *N* (%)	Unintentional pharmaceutical, *N* (%)	Unintentional non-pharmaceutical, *N* (%)
Race				
American Indian/Alaskan Native	44 (57.9)	11 (14.5)	2 (2.6)	3 (4.0)
Asian	82 (48.5)	24 (14.2)	13 (7.7)	6 (3.6)
Black/African	598 (49.8)	186 (15.5)	112 (9.3)	67 (5.6)
Caucasian	2765 (55.8)	576 (11.6)	358 (7.2)	130 (2.6)
Mixed	53 (49.1)	14 (13.0)	9 (8.3)	7 (6.5)
Native Hawaiian or Pacific Islander	13 (72.2)	1 (5.6)	1 (5.6)	1 (5.6)
Other	224 (48.1)	65 (14.0)	39 (8.8)	29 (6.2)
Unknown/uncertain	812 (52.8)	161 (10.5)	125 (8.1)	53 (3.5)
Ethnicity				
Hispanic	485 (51.0)	119 (12.5)	71 (7.5)	60 (6.3)
Not Hispanic	3277 (55.1)	733 (12.3)	450 (7.6)	190 (3.2)
Unknown	829 (50.9)	186 (11.4)	138 (8.5)	46 (2.8)
Gender				
Female	2714 (63.7)	289 (6.8)	323 (7.6)	117 (2.8)
Male	1877 (44.0)	749 (17.6)	336 (7.9)	179 (4.2)

in the miscellaneous category, included the 2C series drugs, 25I-NBOMe, and other unspecified phenethylamines.

Table 15 describes the anticholinergic and antihistamine class (Table 15), and the most commonly reported agent was diphenhydramine (59.1%), which was also one of the most commonly reported agents in the Registry overall, involved in 4.9% of cases. Hydroxyzine was the next most common (14.9%), followed by other first-generation antihistamines chlorpheniramine and doxylamine. Second-generation antihistamines were reported less frequently.

Table 16 presents frequencies for ethanol and the toxic alcohols. Ethanol was again the second most commonly reported agent overall in the Registry ($N = 694$), involved in 8.1% of cases. Among the toxic alcohols, ethylene glycol was the most common (45.5%), followed by isopropanol (32.5%), while methanol was less commonly reported (13.8%).

Table 17 presents the cardiovascular agent class. The 654 cardiovascular agent entries comprised 5.8% of all Registry entries in 2016. In this class, beta adrenergic receptor antagonists (beta-blockers) were the most commonly reported (27.7%), followed by sympatholytics (25.8%), similar to prior years. Metoprolol was the most common beta-blocker. Clonidine (21.6%) was the most common sympatholytic reported with guanfacine also reported but to a much lower extent (4.3%). Together, the calcium channel antagonists comprised 17.3% of the agent class, with amlodipine the most common, followed by diltiazem and verapamil. Angiotensin-converting enzyme (ACE) inhibitors comprised only 8.0% of the cardiovascular agent mentions, with lisinopril accounting for >90% of these. Forty-six cardiac glycoside cases were reported, with all involving digoxin except for two digitoxin cases. Other subgroups of cardiovascular agents were less commonly reported.

Table 18 summarizes the 642 antipsychotic agents reported, which accounted for 5.7% of all Registry entries in 2016. Consistent with prior years, quetiapine was by far the most commonly encountered antipsychotic agent. There were more than three times as many quetiapine cases reported (47.8%) as olanzapine (13.6%), the next most common agent. On its own, quetiapine was listed in 3.6% of all Registry cases in 2016. Aripiprazole was also frequently reported (8.1%), similar to past years. Risperidone, haloperidol, and clozapine together accounted for an additional 16.5% of the antipsychotic agent class.

Table 19 shows anticonvulsants and mood stabilizers. Lithium is considered a unique agent class and reported separately in Table 19. Lithium was reported in 176 cases, representing 2.1% of total Registry cases in 2016. Lamotrigine and valproic acid were the two most commonly reported agents in the anticonvulsants and mood stabilizers class. These were followed by phenytoin, carbamazepine, oxcarbazepine, and topiramate.

Table 20 presents information on envenomations and marine poisonings. This class was dominated by snake envenomations in 2016, consistent with prior years. *Crotalus* spp. were the most commonly reported (34.1%), followed by

Table 9 ToxIC 2016—agent classes

	N (%)[a]
Analgesic	1453 (12.8)
Sedative-hypnotic/muscle relaxant	1339 (11.8)
Antidepressant	1256 (11.1)
Opioid	1118 (9.8)
Sympathomimetic	728 (6.4)
Anticholinergic/antihistamine	704 (6.2)
Ethanol	694 (6.1)
Cardiovascular	654 (5.8)
Antipsychotic	642 (5.7)
Anticonvulsant	370 (3.3)
Envenomation and marine	317 (2.8)
Psychoactive	296 (2.6)
Lithium	176 (1.6)
Diabetic medication	161 (1.4)
Cough and cold products	145 (1.3)
Metals	145 (1.3)
Herbal products/dietary supplements	144 (1.3)
Gases/irritants/vapors/dusts	125 (1.1)
Toxic alcohol	123 (1.1)
Hydrocarbon	94 (0.8)
Caustic	85 (0.7)
Household products	83 (0.7)
Plants and fungi	80 (0.7)
Antimicrobial	73 (0.6)
Other pharmaceutical product	62 (0.5)
Other non-pharmaceutical product	50 (0.4)
Anticoagulant	42 (0.4)
Chemotherapeutic/immunological	42 (0.4)
Insecticide	38 (0.3)
Endocrine	29 (0.3)
Gastrointestinal agents	20 (0.2)
Rodenticide	17 (0.1)
Anesthetic	12 (0.1)
Anti-parkinsonism drugs	9 (0.1)
Amphetamine-like hallucinogen	6 (0.1)
Pulmonary	6 (0.1)
Herbicide	5 (0.0)
WMD/riot agent/radiological	4 (0.0)
Ingested foreign body	3 (0.0)
Fungicide	2 (0.0)
Total	11,352 (100)

[a] Percentages are out of total number of reported agent entries per year; 2519 cases (29.5%) reported multiple agents

Agkistrodon spp. (30.9%), and unspecified snakes (20.6%). Spider envenomations (e.g., *Loxosceles* spp., *Latrodectus* spp., and unspecified spider) were less common, together making up 9.0% of the class.

Table 10 ToxIC 2016 agent entries—analgesics

	N (%)
Acetaminophen	987 (67.9)
Aspirin	197 (13.6)
Ibuprofen	164 (11.3)
Naproxen	39 (2.7)
Salicylic acid	26 (1.8)
Acetylsalicylic acid	15 (1.0)
Diclofenac	4 (0.3)
Miscellaneous[a]	22 (1.5)
Class total	1453 (100)

[a] Includes aminophenazone, unspecified analgesic, carprofen, indomethacin, ketorolac, meloxicam, metamizole (dipyrone), methylsalicylate, unspecified NSAID, phenazopyridine, salicylamide, and salsalate

Table 21 summarizes the psychoactive agent class, which includes marijuana and other cannabinoid receptor agonists, hallucinogens, and dissociatives. Synthetic cannabinoids were the most frequently entered (32.1%), followed by marijuana, lysergic acid diethylamide (LSD), phencyclidine, and gamma hydroxybutyrate. Amphetamine-like hallucinogens are reported with the psychoactives in Table 21.

Table 22 reports data on diabetic medications. Agent frequencies were similar to previous years, with metformin (41.0%) and insulin (24.8%) the most common. These were followed by the sulfonylurea agents: glipizide, glyburide, and glimepiride.

Table 23 presents the metals agent class which was dominated by lead (30.3%), iron (20.7%), and mercury (13.8%), followed by chromium (7.6%) and cobalt (4.8%). The miscellaneous subclass, comprised of 13 different agents, accounted for 15.9% of entries.

Table 24 presents the gases, irritants, vapors, and dusts class. Carbon monoxide was the predominant agent (43.2%), followed hydrogen sulfide (11.2%), and cyanide and smoke (16.8% combined).

Table 25 reports household product exposures. Sodium hypochlorite ≤6% (household bleach) was the most common (31.3%), followed by other cleaning solutions and disinfectants (20.5%) and laundry detergent pods (13.3%). Caustic agents are described separately in Table S4 in the Supplemental Material.

Table 26 presents the diverse species of the plants and fungi agent class. Consistent with prior years, unspecified mold and unknown mushrooms were the predominant agents, followed by *Mitragyna speciosa* (kratom), and a miscellaneous category containing 19 different plant and fungi agents.

Additional agent classes presented in the Supplementary Material include cough and cold products (Table S1), herbal products and dietary supplements (Table S2), hydrocarbons

Table 11 ToxIC 2016 agent entries—sedative-hypnotics/muscle relaxants

	N (%)
Benzodiazepines	704 (52.6)
Alprazolam	276 (20.6)
Clonazepam	207 (15.5)
Lorazepam	99 (7.4)
Diazepam	55 (4.1)
Benzodiazepine unspecified	36 (2.7)
Temazepam	18 (1.3)
Miscellaneous[a]	13 (1.0)
Muscle relaxants	260 (19.4)
Cyclobenzaprine	92 (6.9)
Baclofen	89 (6.6)
Carisoprodol	37 (2.8)
Tizanidine	20 (1.5)
Methocarbamol	12 (0.9)
Metaxalone	7 (0.5)
Miscellaneous[b]	3 (0.2)
Other sedatives	230 (17.2)
Gabapentin	157 (11.7)
Buspirone	29 (2.2)
Pregabalin	18 (1.3)
Phenibut	8 (0.6)
Etizolam	7 (0.5)
Sedative-hypnotic/muscle relaxant unspecified	7 (0.5)
Miscellaneous[c]	4 (0.3)
Non-benzodiazepine agonists ("Z" drugs)	93 (6.9)
Zolpidem	83 (6.2)
Eszopiclone	8 (0.6)
Miscellaneous[d]	2 (0.1)
Barbiturates	52 (3.9)
Butalbital	24 (1.8)
Phenobarbital	20 (1.5)
Miscellaneous[e]	8 (0.6)
Class total	1339 (100)

[a] Includes chlordiazepoxide, clorazepate, midazolam, triazolam, flubromazepam, and oxazepam

[b] Includes orphenadrine and atracurium

[c] Includes propofol and chlomethiazole

[d] Includes eszopiclone and zaleplon

[e] Includes butabarbital, barbiturate unspecified, and pentobarbital

(Table S3), caustics (Table S4); antimicrobials (Table S5), other pharmaceutical products (Table S6), other non-pharmaceutical products (Table S7), anticoagulants (Table S8), chemotherapeutic/immunological agents (Table S9), pesticides, including herbicides, insecticides, rodenticides, and fungicides (Table S10), endocrine agents (Table S11), gastrointestinal agents (Table S12), anesthetics (Table S13), anti-parkinsonism drugs (Table S14), pulmonary

Table 12 ToxIC 2016 agent entries—antidepressants

	N (%)
Other antidepressants	487 (38.8)
Bupropion	260 (20.7)
Trazodone	153 (12.2)
Mirtazapine	57 (4.5)
Vilazodone	5 (0.4)
Miscellaneous[a]	12 (1.0)
Selective serotonin reuptake inhibitors (SSRIs)	431 (34.3)
Sertraline	144 (11.5)
Fluoxetine	100 (8.0)
Citalopram	96 (7.6)
Escitalopram	73 (5.8)
Paroxetine	18 (1.4)
Tricyclic antidepressants (TCAs)	190 (15.1)
Amitriptyline	125 (10.0)
Doxepin	42 (3.3)
Nortriptyline	18 (1.4)
Miscellaneous[b]	5 (0.4)
Serotonin-norepinephrine reuptake inhibitors (SNRIs)	148 (11.8)
Venlafaxine	90 (7.2)
Duloxetine	49 (3.9)
Desvenlafaxine	5 (0.4)
Miscellaneous[c]	4 (0.3)
Class total	1256 (100)

[a] Includes antidepressant unspecified, phenelzine, vortioxetine, levomilnacipran, tranylcypromine, and nefazodone

[b] Includes clomipramine, imipramine, and desipramine

[c] Includes fluvoxamine

agents (Table S15), weapons of mass destruction/riot/radiological agents (Table S16), and ingested foreign bodies (Table S17).

Clinical Signs and Symptoms

Table 27 summarizes the 3134 clinical toxidromes reported in 2016. The frequencies of reported toxidromes were similar to past years with sedative-hypnotic the most common (14.9%), followed by anticholinergic (7.4%), sympathomimetic (4.5%), and opioid (4.4%).

Table 28 summarizes the 2627 major vital sign abnormalities recorded in 2016. Tachycardia was the most common (12.1%), followed by hypotension (8.0%), bradycardia (4.6%), and several others affecting <4% of total cases. Note that some cases reported more than one major vital sign abnormality. Additionally, cases may include more than one of the other signs/symptom categories described below.

Table 29 summarizes the neurological signs and symptoms reported in 2016. While the overall numbers of cases with neurological signs and symptoms increased from previous

Table 13 ToxIC 2016 agent entries—opioids

	N (%)
Heroin	316 (28.3)
Oxycodone	199 (17.8)
Methadone	99 (8.9)
Opioid unspecified	90 (8.1)
Tramadol	87 (7.8)
Hydrocodone	86 (7.7)
Morphine	57 (5.1)
Buprenorphine	47 (4.2)
Fentanyl	46 (4.1)
Codeine	36 (3.2)
Hydromorphone	19 (1.7)
Loperamide	9 (0.8)
Oxymorphone	7 (0.6)
Naltrexone	5 (0.4)
Miscellaneous[a]	15 (1.3)
Class total	1118 (100)

[a] Includes 3-methylfentanyl, desomorphine, naloxone, pentazocine, propoxyphene, remifentanil, tapentadol, and U47700 (designer opioid)

years, the order remained similar, with coma/central nervous system depression the most common (34.7%), followed by agitation (16.7%) and delirium (11.8%).

Table 14 ToxIC 2016 agent entries—sympathomimetics

	N (%)
Cocaine	250 (34.3)
Methamphetamine	187 (25.7)
Amphetamine	90 (12.4)
Methylphenidate	48 (6.6)
Dextroamphetamine	32 (4.4)
Methylenedioxy-*N*-methamphetamine	31 (4.3)
Lisdexamfetamine	24 (3.3)
Phenylephrine	10 (1.4)
Pseudoephedrine	9 (1.2)
Phentermine	8 (1.1)
Cathinone	6 (0.8)
Phentermine	7 (1.2)
Sympathomimetic unspecified	5 (0.7)
Miscellaneous[a]	28 (3.8)
Class total	728 (100)

[a] Includes 25I-NBOMe, atomoxetine, clenbuterol, dexmethylphenidate, ephedrine, 2C series drugs, epinephrine, 2,5-dimethoxy-4-bromophenethylamine, 4-fluoroamphetamine, 6-(2-Aminopropyl)benzofuran, butylone, *N*-ethylhexedrone, norepinephrine, phenylethylamine designer drug unspecified, prolintane, and tetrahydrozoline

Table 15 ToxIC 2016 agent entries—anticholinergics and antihistamines

	N (%)
Diphenhydramine	416 (59.1)
Hydroxyzine	105 (14.9)
Chlorpheniramine	34 (4.8)
Doxylamine	32 (4.5)
Benztropine	29 (4.1)
Promethazine	16 (2.3)
Loratadine	15 (2.1)
Cetirizine	9 (1.3)
Dicyclomine	6 (0.9)
Antihistamine unspecified	5 (0.7)
Cyproheptadine	5 (0.7)
Miscellaneous[a]	32 (4.5)
Class total	704 (100)

[a] Includes anticholinergic unspecified, atropine, belladonna, brompheniramine, cyclopentolate, dimenhydrinate, fexofenadine, glycopyrrolate, hyoscyamine, meclizine, oxybutynin, pyrilamine, scopolamine, trihexyphenidyl, and triprolidine

Table 30 summarizes the cardiovascular and pulmonary signs and symptoms reported in 2016. Although the total number of cardiovascular and pulmonary signs reported was higher this year than in previous years, the order remained similar, with prolonged QTc (≥500ms) the most common cardiovascular sign (5.6%), followed by prolonged QRS (≥120 ms) (1.8%). The most common pulmonary sign was respiratory depression (11.1%).

Table 31 summarizes signs and symptoms involving other organ systems. As in the past years, metabolic signs (e.g., elevated anion gap, metabolic acidosis) were common, reported in 12.2% of cases. Renal and musculoskeletal signs (e.g., rhabdomyolysis, acute kidney injury) were also common

Table 16 ToxIC 2016 agent entries— ethanol and toxic alcohols

	N (%)
Ethanol[a]	694 (100)
Non-ethanol alcohols and glycols	
Ethylene glycol	56 (45.5)
Isopropanol	40 (32.5)
Methanol	17 (13.8)
Propylene glycol	4 (3.3)
Miscellaneous[b]	6 (4.9)
Class total	123 (100)

[a] Ethanol is considered a separate agent class

[b] Includes acetone, denatured alcohol non-ethanol, diethylene glycol, glycol ethers, and toxic alcohol unspecified

Table 17 ToxIC 2016 agent entries—cardiovascular

	N (%)
Beta blockers	181 (27.7)
Metoprolol	70 (10.7)
Propranolol	56 (8.6)
Atenolol	24 (3.7)
Carvedilol	16 (2.4)
Labetalol	7 (1.1)
Miscellaneous[a]	8 (1.2)
Sympatholytics	169 (25.8)
Clonidine	141 (21.6)
Guanfacine	28 (4.3)
Calcium channel antagonists	113 (17.3)
Amlodipine	63 (9.6)
Diltiazem	23 (3.5)
Verapamil	18 (2.8)
Nifedipine	8 (1.2)
Miscellaneous[b]	<5 (<0.8)
Angiotensin-converting enzyme (ACE) inhibitors	52 (8.0)
Lisinopril	47 (7.2)
Miscellaneous[c]	5 (0.8)
Cardiac glycosides	46 (7.0)
Digoxin	44 (6.7)
Digitoxin	2 (0.3)
Other antihypertensives and vasodilators	32 (4.9)
Prazosin	16 (2.4)
Miscellaneous[d]	16 (2.4)
Antidysrhythmics and other cardiovascular agents	27 (4.1)
Atorvastatin	8 (1.2)
Simvastatin	6 (1.0)
Miscellaneous[e]	13 (2.0)
Diuretics	25 (3.8)
Hydrochlorothiazide	16 2.4)
Furosemide	5 (0.8)
Miscellaneous[f]	4 (0.6)
Angiotensin receptor blockers	9 (1.4)
Losartan	5 (0.8)
Miscellaneous[g]	4 (0.6)
Class total	654 (100)

[a] Includes nebivolol, bisoprolol, nadolol, and timolol

[b] Includes nicardipine

[c] Includes benazepril, enalapril, and quinapril

[d] Includes hydralazine, nitroprusside, isosorbide, nitroglycerin, terazosin, alkyl nitrite, doxazosin, and minoxidil

[e] Includes flecainide, sotalol, amiodarone, midodrine, cardiovascular agent unspecified, quinidine, pravastatin

[f] Includes chlorthalidone, acetazolamide, spironolactone

[g] Includes valsartan, irbesartan, olmesartan

(10.3%), followed by hematological (6.2%), gastrointestinal/hepatic (5.3%), and dermal (3.4%) signs and symptoms.

Table 18 ToxIC 2016 agent entries—antipsychotics

	N (%)
Quetiapine	307 (47.8)
Olanzapine	87 (13.6)
Aripiprazole	52 (8.1)
Risperidone	41 (6.4)
Haloperidol	39 (6.1)
Clozapine	26 (4.0)
Lurasidone	20 (3.1)
Ziprasidone	17 (2.6)
Chlorpromazine	15 (2.3)
Paliperidone	9 (1.4)
Perphenazine	7 (1.1)
Fluphenazine	6 (0.9)
Miscellaneous[a]	16 (2.5)
Class total	642 (100)

[a] Includes antipsychotic unspecified, asenapine, brexpiprazole, loxapine, penfluridol, prochlorperazine, thiothixene, and trifluoperazine

Fatalities

Tables 32 and 33 present data on ToxIC 2016 cases involving exposures which resulted in fatalities, with Table 32 including cases involving single agent exposures and Table 33 including cases involving multiple agents. Table S18 in the Supplementary Information summarizes information on fatality cases with no suspected toxicologic exposure, or an unknown exposure(s).

The number of fatalities increased again in 2016 to 126, along with an increased percentage of cases reporting a fatality (1.5%), up from 98 fatalities (1.2%) in 2015, and 89 fatalities (1.0%) in 2014 [2, 7]. Of these 126 fatalities, 63 (0.7%)

Table 19 ToxIC 2016 agent entries—anticonvulsants and mood stabilizers, and lithium

	N (%)
Lithium[a]	176 (100)
Lamotrigine	100 (27.0)
Valproic acid	98 (26.5)
Phenytoin	56 (15.1)
Carbamazepine	42 (11.4)
Topiramate	29 (7.8)
Oxcarbazepine	20 (5.4)
Levetiracetam	9 (2.4)
Miscellaneous[b]	16 (4.3)
Class total	370 (100)

[a] Lithium is considered a separate agent class

[b] Includes anticonvulsant unspecified, divalproex, fosphenytoin, lacosamide, and zonisamide

Table 20 ToxIC 2016 agent entries—envenomations and marine poisonings

	N (%)
Crotalus spp.	106 (34.1)
Agkistrodon spp.	96 (30.9)
Snake unspecified	64 (20.6)
Loxosceles spp.	13 (4.2)
Latrodectus spp.	10 (3.2)
Centuroides spp.	5 (1.6)
Hymenoptera	5 (1.6)
Spider unspecified	5 (1.6)
Miscellaneous[a]	7 (2.3)
Class total	311 (100)

[a] Includes *Naja nigricinta*, *Vipera palaestinae*, *Micrurus* spp., scorpion unspecified, and stingray

involved single agent exposures and 35 (0.4%) cases involved multiple agent exposures. The remaining 28 (0.3%) fatalities were categorized as not a toxicological exposure, or unknown with respect to toxicity and presentation and are presented in Table S18.

Six fatalities (four females, two males) involved pediatric (age 0–18 year) patients. All six were adolescents, with ages ranging from 14 to 17 years, constituting 4.8% of fatalities. Five of these were intentional pharmaceutical exposures, with some intent to self-harm, and four were reported as definitive suicide attempts. An additional case reported toxicology involvement to assist with interpretation of lab data and evaluation of malicious or criminal intent. Three pediatric fatalities involved single agents (bupropion, cocaine, and diphenhydramine) and three involved multiple agents (acetaminophen, bupropion, ethanol, fluoxetine, ibuprofen, meclizine, and quetiapine). Life support measures were withdrawn in five of the six pediatric fatality cases. The sixth case is reported as unknown whether life support was withdrawn in a 16-year-old male with an exposure to acetaminophen and ethanol, and no treatment interventions are listed. This entry was categorized as misuse or abuse of a substance by taking higher doses than recommended of an over the counter product without an attempt at self-harm. No further details were provided to describe the lack of interventions or treatments recorded such as pronounced on arrival, or family or religious preference.

Table 21 ToxIC 2016 agent entries—psychoactives

	N (%)
Cannabinoid synthetic	95 (31.5)
Marijuana	88 (29.1)
LSD	22 (7.3)
Phencyclidine	20 (6.6)
Gamma hydroxybutyrate	16 (5.3)
Cannabinoid non-synthetic[a]	12 (4.0)
Ketamine	11 (3.6)
Nicotine	9 (3.0)
Molly-amphetamine-like hallucinogen[b]	6 (2.0)
Miscellaneous[c]	23 (7.6)
Class total	302 (100)

[a] The cannabinoid nonsynthetic group refers to exposures to unspecified naturally occurring cannabinoids, such as cannabis extracts or cannabidiol

[b] Amphetamine-like hallucinogens are presented with psychoactives for brevity, though listed as an individual Registry class

[c] Includes 1-propionyl-lysergic acid diethylamide (1P-LSD), 3-methoxyphencyclidine, dimethyltryptamine (DMT), donepezil, gamma butyrolactone, hallucinogen unspecified, hallucinogenic amphetamines, methylenedioxymethamphetamine, methylone, pharmaceutical tetrahydrocannabinol (THC), psychoactive unspecified, and varenicline

Table 22 ToxIC 2016 agent entries—diabetic medications

	N (%)
Metformin	66 (41.0)
Insulin	40 (24.8)
Glipizide	26 (16.1)
Glyburide	14 (8.7)
Glimepiride	8 (5.0)
Miscellaneous[a]	7 (4.3)
Class total	161 (100)

[a] Includes empagliflozin, exenatide, gliclazide, and saxagliptin

Among the single agent fatalities (all ages), there were four deaths attributed to ethanol; of these, three were intubated and mechanically ventilated and received either continuous renal replacement or hemodialysis. Eight single agent fatalities (age range 21–51 years) were attributed to heroin and one to fentanyl (a 19-year-old). Of the multiple agent fatalities, six involved heroin and three involved fentanyl. Fourteen fatalities overall were single

Table 23 ToxIC 2016 agent entries—metals

	N (%)
Lead	44 (30.3)
Iron	30 (20.7)
Mercury	20 (13.8)
Chromium	11 (7.6)
Cobalt	7 (4.8)
Arsenic	5 (3.4)
Copper	5 (3.4)
Miscellaneous[a]	23 (15.9)
Class total	145 (100)

[a] Includes manganese, metal unspecified, cadmium, silver, titanium, antimony, barium, magnesium, nickel, selenium, thorium, uranium, and zinc sulfate

Table 24 ToxIC 2016 agent entries—gases, irritants, vapors, and dusts

	N (%)
Carbon monoxide	54 (43.2)
Hydrogen sulfide	14 (11.2)
Cyanide	11 (8.8)
Smoke	10 (8.0)
Chlorine	5 (4.0)
Gas/irritant/vapor/dust unspecified	5 (4.0)
Miscellaneous[a]	26 (20.8)
Class total	125 (100)

[a] Includes petroleum vapors, silica, chloramine, diesel exhaust, dust, ethylene oxide, sewer gas, acetonitrile, duster (canned air), ethylene, natural gas, nitric oxide, ozone, plastic fumes, polyurethane vapors, welding fumes, and vaping NOS

agent exposures to opioids, while 15 multiple agent fatalities involved one or more opioids including 4 cases involving a combination of cocaine with heroin or other opioid.

Life support measures were withdrawn in 60 (61.2%) of the fatalities related to a toxicologic exposure (single or multi-agent), with brain death confirmed in 26 (43.3%). The 60 patients ranged in age from 14 to 80 years (including 5 pediatric patients), with two patients of unknown age. The mean and median ages for those with life support withdrawn were 44.6 and 43.5 years, respectively, with a sex distribution of 55.0% male and 45.0% female.

Adverse Drug Reactions

Table 34 presents information on adverse drug reactions (ADRs). In 2016, there were 320 cases (3.8% of Registry cases) that were categorized as ADRs, defined as any unintended response to a medication as used in standard therapeutic dosing. There were 455 total agent entries with 164 unique agents. Some cases reported multiple agents, possibly reflecting drug-drug interactions. The strength of association between the reported agent and the clinical presentation was recorded as definitive by rechallenge in 4.7% of cases, probable in 72.8%, and possible in 22.5%. The most frequently recorded drugs in ADR cases in 2016 were lithium (11.9%) and digoxin (5.9%).

Table 25 ToxIC 2016 agent entries—household products

	N (%)
Sodium hypochlorite ≤6%	26 (31.3)
Cleaning solutions and disinfectants	17 (20.5)
Laundry detergent pod	11 (13.3)
Ammonia ≤10%	6 (7.2)
Paint	5 (6.0)
Miscellaneous[a]	18 (21.7)
Class total	83 (100)

[a] Includes deodorants and antiperspirants, dishwasher detergent, dishwasher detergent pod, flower food, hair product, hand sanitizer unspecified, household product unspecified, mouthwash unspecified, perfume, phenylenediamine (hair dye), soaps and detergents, sunscreens, and windshield washer fluid

Table 26 ToxIC 2016 agent entries—plants and fungi

	N (%)
Mold unspecified	33 (41.3)
Mushroom, other/unknown	9 (11.3)
Mitragyna speciosa (kratom)	6 (7.5)
Mushroom, psilocibin	4 (5.0)
Valerian root	4 (5.0)
Miscellaneous[a]	24 (30.0)
Class total	80 (100)

[a] Includes aconitum, *Agastache scrophulariifolia* (purple giant hyssop), *Amanita muscaria*, *Brugmansia* (angels trumpet), *Convallaria majalis* (lily of the valley), *Crataegus* (hawthorn), *Datura inoxia* (moonflower, thornapple), *Dieffenbachia*, *Ganoderma* mushroom, kola nut, kombucha tea, *Nerium oleander*, petasites (butterbur), *Phytolacca americana* (pokeweed), *Piper methysticum* (kava), plants and fungi unspecified, poppy seeds (*Papaver*), *Ricinus communis* (castor beans), and *Sanseviera* (Snake plant, Mother in Laws tongue)

Table 27 ToxIC 2016 cases—toxidromes

	N (%)[a]
Sedative-hypnotic	1261 (14.9)
Anticholinergic	629 (7.4)
Sympathomimetic	386 (4.5)
Opioid	378 (4.4)
Serotonin syndrome	259 (3.0)
Alcoholic ketoacidosis	87 (1.0)
Sympatholytic	50 (0.6)
Washout syndrome	36 (0.4)
NMS	19 (0.2)
Cholinergic	16 (0.2)
Overlap syndromes (MCS, chronic fatigue, etc.)	10 (0.1)
Miscellaneous[b]	8 (0.1)
Total	3134 (36.7)

NMS neuroleptic malignant syndrome

[a] Percentage equals number cases reporting specific toxidrome relative to total number of Registry cases in 2016 (*N* = 8529)

[b] Includes anticonvulsant hypersensitivity and fume fever

Table 28 ToxIC 2016 cases—major vital sign abnormalities

	N (%)[a]
Tachycardia (HR >140)	1031 (12.1)
Hypotension (systolic BP < 80 mmHg)	684 (8.0)
Bradycardia (HR < 50)	393 (4.6)
Bradypnea (RR < 10)	249 (2.9)
Hypertension (systolic BP > 200 mmHg and/or diastolic BP > 120 mmHg)	224 (2.6)
Hyperthermia (temperature > 105 °F)	46 (0.5)
Total	2627 (30.8)[b]

HR heart rate, *BP* blood pressure, *RR* respiratory rate

[a] Percentage equals the number of cases relative to the total number of Registry cases in 2016 (*N* = 8259)

[b] Total reflects cases reporting at least one major vital sign abnormality; cases may be associated with more than one major vital sign abnormality

Treatment

In 2016, there were 3047 cases (35.7% of total Registry cases) with at least one antidote administered, and 3540 antidotes given overall (Table 35). Similar to prior years, N-acetylcysteine was the most common, accounting for more than one quarter of antidotes given in 2016 (27.5%), followed by naloxone/nalmefene (19.9%), and sodium bicarbonate (11.9%). In 2016, 2.7% of Registry cases reported antivenom therapy, with the vast majority of these (96.1%) receiving Crotalidae polyvalent immune fab (ovine), again reflecting the presence of the North American Snake Bite Registry within the overall Registry (Table 36).

Tables 37 and 38, respectively, summarize the pharmacological and non-pharmacological supportive care intervention frequencies in 2016. A total of 3830 pharmacological and 4522 non-pharmacological supportive care interventions were reported. There were 2741 cases (32.1% of total Registry cases) reporting at least one form of pharmacologic treatment and 3508 cases (41.1% of total Registry cases) reporting at least one non-pharmacological intervention. Some cases involved more than one form of treatment. Similar to past years, benzodiazepines were used in half of the pharmacological interventions, followed by opioids (10.8%), vasopressors (10.3%), and antipsychotics (7.2%). Of the non-pharmacological interventions, intravenous fluid resuscitation was the most common (70.3%), followed by intubation and ventilatory management (25.1%).

Table 39 summarizes the 31 chelation therapy interventions, which accounted for 0.4% of total Registry cases in 2016. Deferoxamine and dimercaptosuccinic acid (DMSA) were reported in equal numbers.

Table 40 summarizes the 334 decontamination procedures reported in the Registry in 2016. There were 318 cases (3.7% of total Registry cases) in which at least one decontamination procedure was performed. Activated charcoal was most common (79.3%), followed by whole bowel irrigation (9.9%), and external irrigation (8.7%). Gastric lavage was uncommon with only seven cases (2.1%) reported.

Table 41 reports enhanced elimination procedures. Enhanced elimination was performed in 280 cases (3.3% of total cases), with some cases reporting more than one, for a total of 321 reported treatments. Hemodialysis for toxin removal (32.1%) and urinary alkalinization (29.3%) were the most common. Hemodialysis for other indications comprised an additional 19.0% of enhanced elimination procedures.

Table 29 ToxIC 2016 cases—neurological signs and symptoms

	N (%)[a]
Coma/CNS depression	2959 (34.7)
Agitation	1421 (16.7)
Delirium	1005 (11.8)
Hyperreflexia/myoclonus/tremor	635 (7.4)
Seizures	459 (5.4)
Hallucinations	366 (4.3)
Weakness/paralysis	142 (1.7)
Dystonia/rigidity/extrapyramidal symptoms	112 (1.3)
Numbness/Paresthesia	79 (0.9)
Peripheral neuropathy	25 (0.3)
Total	4970 (58.3)[a,b]

CNS central nervous system

[a] Percentage equals number of cases relative to total number of Registry cases in 2016 (*N* = 8529)

[b] Total reflects cases reporting at least one neurological symptom; cases may be associated with more than one neurological symptom

Table 30 ToxIC 2016 cases—cardiovascular and pulmonary signs

	N (%)[a]
Cardiovascular	
Prolonged QTc (≥500 ms)	480 (5.6)
Prolonged QRS (≥120 ms)	150 (1.8)
Ventricular dysrhythmia	102 (1.2)
Myocardial injury or infarction	61 (0.7)
AV block (>1st degree)	41 (0.5)
Total	834 (9.8)[b]
Pulmonary	
Respiratory depression	946 (11.1)
Aspiration pneumonitis	182 (2.1)
Acute lung injury/ARDS	117 (1.4)
Asthma/reactive airway disease	60 (0.7)
Total	1305 (15.3)[b]

ARDS acute respiratory distress syndrome

[a] Percentage equals number cases reporting signs of symptoms relative to total number of Registry cases in 2016 (*N* = 8529)

[b] Total reflects cases reporting at least one cardiovascular or pulmonary symptom; cases may be associated with more than one symptom

Table 31 ToxIC 2016 cases—clinical signs—other organ systems

	N (%)[a]
Metabolic	
Elevated anion gap (>20)	459 (5.4)
Metabolic acidosis (pH <7.2)	387 (4.5)
Hypoglycemia (glucose <50 mg/dL)	126 (1.5)
Elevated osmole gap (>20)	61 (0.7)
Total	1033 (12.1)[b]
Gastrointestinal/hepatic	
Hepatotoxicity (AST ≥1000 IU/L)	296 (3.5)
Pancreatitis	64 (0.8)
Gastrointestinal bleeding	49 (0.6)
Corrosive injury	42 (0.5)
Intestinal ischemia	5 (0.1)
Total	456 (5.3)[b]
Hematological	
Coagulopathy (PT >15 s)	199 (2.3)
Leukocytosis (WBC >20 K/μL)	131 (1.5)
Thrombocytopenia (platelets <100 K/μL)	102 (1.2)
Hemolysis (Hgb <10 g/dL)	56 (0.7)
Pancytopenia	21 (0.2)
Methemoglobinemia (MetHgb ≥2%)	18 (0.2)
Total	527 (6.2)[b]
Renal/musculoskeletal	
Rhabdomyolysis (CPK >1000 IU/L)	489 (5.7)
Acute kidney injury (creatinine >2.0 mg/dL)	386 (4.5)
Total	875 (10.3)[b]
Dermatological	
Rash	165 (1.9)
Blister/bullae	71 (0.8)
Necrosis	31 (0.4)
Angioedema	25 (0.3)
Total	292 (3.4)[b]

AST aspartate aminotransferase, *PT* prothrombin time, *WBC* white blood cells, *Hgb* hemoglobin, *CPK* creatine phosphokinase

[a] Percentage equals the number of cases reporting specific clinical signs compared to the total number of Registry cases in 2016 (*N* = 8529)

[b] Total reflects cases reporting at least one sign in the category; cases may be associated with more than one symptom

Discussion

This report summarizes the seventh year of data collected in ACMT's ToxIC Case Registry. Although the Registry is not population based, it is a large source of information that can be used in conjunction with data from health agencies, poison centers, and other sources to produce a more detailed picture of poisoning trends and their public health implications. Novel exposure surveillance data from the Registry is not reported in this Annual Report, but is being analyzed, with results to be published separately. The most common agent classes, types of encounters, toxidromes, and treatments were similar to prior years. Some broad trends, both within the Registry itself and within the larger national context, are discussed.

Opioids

Opioid fatalities reported in the ToxIC Registry over the past few years mirror the national trends of steadily increasing age-adjusted death rates (per 100,000 population) from heroin and synthetic opioids other than methadone (e.g., fentanyl, tramadol) according to National Vital Statistics System data [12, 13]. In 2016, heroin-related deaths in ToxIC were the highest reported since the Registry's inception, increasing both in absolute number and in percentage of all fatalities cases—11.1% of fatalities in 2016 versus 4.1% in 2015 and 6.7% in 2014 [2, 7]. Fentanyl-related deaths also increased in 2016 with four reported cases (3.2%), up from 0.0% in 2015 and 1.1% in 2014 [2, 7]. The total number of opioid-related fatalities (all agents) in ToxIC increased to 29 cases (23.0% of total fatalities) in 2016, compared to 14.2% in 2015 and 18.0% in 2014 [2, 7].

Deaths related to illicit street opioid use may be more complicated to ascribe definitively to heroin or to fentanyl and newer fentanyl derivatives since testing for these agents is not routinely conducted. Thus, it is possible that some of the deaths attributed to heroin in the ToxIC Registry may be related to newer synthetic opioids. Of note, the number of ToxIC cases (fatality and non-fatality) involving an "unspecified opioid" increased to 8.1% of total opioid cases in 2016, compared to 6.5, 4.1, and 0.6% in 2015, 2014, and 2013, respectively [2, 7, 8]. In addition, two fatalities were attributed to unspecified opioids as single agents and one to unspecified opioids with cocaine in 2016, in contrast to zero deaths from unspecified opioids in 2014 and 2015 [2, 7]. One possible explanation for the rise in unspecified opioid case reporting may be the difficulty in clinically identifying the specific illicit opioid responsible.

The increase in ToxIC opioid cases (both fatal and non-fatal) in 2016 likewise reflects the national opioid crisis. The percentage of opioid cases vs. total Registry cases increased from 8.8% in 2015 to 9.8% in 2016 [2]. As in 2015, heroin, oxycodone, and methadone were the most commonly reported opioids in 2016, each up slightly from 2015 in terms of absolute numbers and percent of total opioid cases [2]. In addition, several designer opioids—3-methylfentanyl, remifentanil, and U-47700—were reported for the first time in ToxIC in 2016. Of all the opioids reported, two decreased notably from 2015 to 2016: buprenorphine, down to 4.2% from 7.5% of opioid cases in 2015, and tramadol, down to 7.8% from 10.5% of opioid cases in 2015 [2].

Table 32 ToxIC 2016 fatality cases with known toxicological exposure, single agent

Age/sex[a]	Agents involved	Clinical findings	Life support withdrawn	Brain death confirmed	Treatment[b]
40M	Acetaminophen	HT, CNS, MA, AG, HPT, PNC, CPT, PLT, AKI, RBM	No	Unknown	NAC, vitamin K, vasopressors, anticonvulsants, neuromuscular blockers, opioids, continuous renal replacement, intubation, IV fluids
41F	Acetaminophen	TC, RD, AGT, CNS, AG, HPT, PNC, HYS, AKI, RBM	Yes	Unknown	NAC, vitamin K, benzodiazepines, intubation, IV fluids
21F	Heroin	HT, BC, BP, VD, RD, CNS, MA	Yes	Yes	Physostigmine, vasopressors, antiarrhythmics, CPR, intubation, IV fluids, therapeutic hypothermia
41F	Acetaminophen	HT, RD, CNS, MA, AG, HPT, CPT, WBC, RBM	Yes	No	NAC, $NaHCO_3$, vitamin K, vasopressors, anticonvulsants, benzodiazepines, opioids, continuous renal replacement, intubation, IV fluids
43M	Methanol	HT, QRS, RD, CNS, MA, AG, OG, CPT, AKI, RBM	Yes	Yes	Folate, fomepizole, hemodialysis, intubation, IV fluids
29F	Acetaminophen	HT, TC, CNS, HGY, HPT, CPT, AKI	Yes	No	NAC, $NaHCO_3$, vitamin K, benzodiazepines, glucose, neuromuscular blockers, opioids, vasodilators, hemodialysis, continuous renal replacement, intubation, IV fluids, transfusion
52M	Ethanol	HT, TC, MA, AG, HPT, PNC, PLT, AKI	Unknown	Unknown	NAC, vasopressors, continuous renal replacement, cardioversion, intubation, IV fluids
35F	Amitriptyline	HT, TC, BP, VD, QRS, RD, CNS, MA, AG, HPT, AKI	Yes	Yes	Naloxone, $NaHCO_3$, vasopressors, CPR, intubation, IV fluids
54M	Ethanol	CNS	Yes	Yes	Fomepizole, NAC, hemodialysis, intubation, transfusion
80M	Carbon monoxide	HT, AVB, RD, CNS, WKN, MA, OTH1	Yes	No	Hydroxocobalamin, vasopressors, intubation, IV fluids
77M	Metoprolol	HT, BC, AVB, RD, CNS	Yes	No	Insulin-euglycemic therapy, vasopressors, glucose, intubation, IV fluids
51F	Acetaminophen	HT, TC, BC, BP, VD, ALI, RD, CNS, MA, AG, HPT, HYS, CPT, PLT, WBC, AKI	Yes	No	Lipid resuscitation, methylene blue, NAC, $NaHCO_3$, vasopressors, intubation, transfusion
51F	Heroin	HT, BP, RD, CNS, HPT, WBC, RBM	Yes	Yes	$NaHCO_3$, vasopressors, benzodiazepines, intubation, IV fluids
24F	Acetaminophen	HT, VD, CNS, HGY, MA, AG, HPT, PNC, PLT	Yes	No	NAC, vasopressors, benzodiazepines, glucose, continuous renal replacement, intubation, IV fluids, therapeutic hypothermia
63F	Acetaminophen	HT, BC, BP, VD, ALI, RD, CNS, MA, AG, HPT, PNC, INT, CPT, PLT, WBC	No	No	NAC, vasopressors, CPR, intubation, IV fluids
60M	Colchicine	HT, VD, MA, AG, CPT, PLT, PCT, WBC	No	No	Vasopressors, antiarrhythmics, continuous renal replacement, intubation, IV fluids
51M	Metformin	HT, TC, ALI, MA, AG, RBM	Unknown	Unknown	Hemodialysis, intubation
83F	Diltiazem	HT, BC, CNS, MA, AG,	Unknown	Unknown	Glucagon, insulin-euglycemic therapy, lipid resuscitation, vasopressors, intubation, IV fluids
40F	Heroin	BP, CNS, MA	Yes	Yes	NAC, naloxone,
57M	Bupropion	VD, AP, ALI, CNS, SZ, AKI	No	No	Lipid resuscitation, $NaHCO_3$, vasopressors, benzodiazepines, CPR, intubation, IV fluids
19M	Fentanyl	RD, CNS	Yes	Yes	Naloxone, CPR, intubation
14F	Diphenhydramine	HT, VD, QTc, QRS, CNS, SZ, MA, AG	Yes	No	Vasopressors, antiarrhythmics, anticonvulsants, benzodiazepines, intubation, IV fluids
63F	Doxepin	RD, CNS, AKI	Yes	No	Glucagon, $NaHCO_3$, intubation, IV fluids
22F	Acetaminophen	HT, TC, RD, CNS, SZ, MA, AG, HPT, CPT	Yes	Yes	NAC, vasopressors, anticonvulsants, benzodiazepines, intubation, IV fluids,
14F	Bupropion	HT, QRS, ALI, RD, CNS, SZ, MA, AKI, RBM	Yes	Unknown	Insulin-euglycemic therapy, lipid resuscitation, $NaHCO_3$, vasopressors, urinary alkalinization, CPR, intubation, IV fluids, therapeutic hypothermia
60F	Quinidine	MET	No	No	Calcium, methylene blue, $NaHCO_3$, vitamin K, vasopressors, hypoglycemia, exchange transfusion, IV fluids, transfusion
52M	Sevoflurane	HTN, TC, HYT, VD, QTc, QRS, EPS	Yes	No	Dantrolene, $NaHCO_3$, intubation, IV fluids
32M	Cyanide	HT, TC, CNS, MA	No	No	Hydroxocobalamin, intubation, IV fluids
19F	Acetaminophen	None listed	No	No	NAC, IV fluids
47M	Hydromorphone	AP	No	No	NAC, IV fluids

Table 32 (continued)

Age/sex[a]	Agents involved	Clinical findings	Life support withdrawn	Brain death confirmed	Treatment[b]
65F	Digoxin	HT, BC, WKN	Yes	No	Digoxin Fab, vasopressors, IV fluids
60F	Amitriptyline	HT, TC, VD, QRS, RAD, ALI, RD,	Yes	No	$NaHCO_3$, vasopressors, intubation, intubation, IV fluids
17F	Cocaine	TC, RD, AGT, CNS, DLM, SZ, MA, AG, HPT, HYS, CPT, PLT, WBC, AKI	Yes	No	Vasopressors, anticonvulsants, benzodiazepines, glucose, opioids, hemodialysis, CPR, intubation, IV fluids, transfusion
32M	Cyanide	HT, VD, RAD, AGT, CNS, MA	No	No	Hydroxocobalamin, thiosulfate, vasopressors, CPR, intubation, IV fluids
51M	Warfarin	CNS, CPT, WBC	Yes	Yes	Anticoagulant reversal, anticonvulsants, neuromuscular blockers, intubation
33M	Hydrogen sulfide	HT, TC, VD, ALI, RD, CNS, MA	Yes	Unknown	Vasopressors, antiarrhythmics, benzodiazepines, CPR, cardioversion, intubation, IV fluids
61M	Ethanol	HT, DLM, HCN, HPT, PNC, HYS, PLT	Yes	Unknown	Calcium, folate, octreotide, thiamine, benzodiazepines, IV fluids, transfusion
21F	Acetaminophen	HT, BC, VD, ALI, RD, CNS, MA, AG, HPT, CPT, AKI	No	No	NAC, $NaHCO_3$, vasopressors, antiarrhythmics, benzodiazepines, CPR, cardioversion, intubation, IV fluids
45M	Codeine	HT, BC, VD, RD, CNS, MA, AG,	Yes	Yes	NAC, $NaHCO_3$, vasopressors, antiarrhythmics, anticonvulsants, beta blockers, opioids, CPR, cardioversion, intubation, IV fluids, therapeutic hypothermia
>89M	Carbon monoxide	HT, VD, RD, CNS, AG	No	No	Thiosulfate, vasopressors, intubation, IV fluids
68M	Digoxin	HT, QRS, RD, AGT, CNS	Yes	Unknown	Digoxin Fab, pacemaker
39F	Gabapentin	HT, VD, QTc, MI, RD, CNS, MA, AG, HPT, MI, WBC, AKI, RBM	Yes	No	Vasopressors, antiarrhythmics, CPR, intubation, therapeutic hypothermia
38F	Acetaminophen	HT, TC, MI, ALI, CNS, MA, AG, HPT, GIB, HYS, CPT, PLT, PCT, AKI, RBM	Yes	Unknown	NAC, $NaHCO_3$, vitamin K, vasopressors, glucose, continuous renal replacement, intubation, IV fluids
68M	Chlorine	HT, QTc, MI, ALI, RD, CNS	No	No	Vasopressors, neuromuscular blockers, intubation, IV fluids
68M	Copper	HT, CRV, GIB, MET, WBC, AKI	No	No	BAL, penicillamine, vasopressors, hemodialysis, continuous renal replacement, CPR, intubation, IV fluids, transfusion
46M	Amlodipine	HT, RAD, CNS, MA, AKI	Yes	No	Lipid resuscitation, methylene blue, $NaHCO_3$, thiamine, vitamin K, vasopressors, bronchodilators, antiarrhythmics, benzodiazepines, neuromuscular blockers, opioids, steroids, intubation, IV fluids
24M	Opioid unspecified	VD, QTc, QRS, MI, AP, RD, CNS, MA,	Yes	Yes	None listed
74M	Ciguatera	PST, WKN	Yes	No	None listed
27M	Morphine	HT, BP, MI, RAD, ALI, RD, CNS, MA, AG. CPT, AKI, RBM	Yes	Yes	Naloxone, vasopressors, CPR, intubation, IV fluids, therapeutic hypothermia
38M	Heroin	HT, TC, MI, ALI, CNS, NP, MA, WBC	Unknown	Unknown	Folate, naloxone, vasopressors, intubation, IV fluids
31M	Heroin	HT, VD, QRS, MI, RAD, RD, CNS, MA, AG, AKI	Yes	Yes	None listed
58M	Amphetamine	QRS, QTc, AGT, MA, AG, OG, INT, PLT, AKI	Yes	Unknown	Fomepizole, vasopressors, hemodialysis, continuous renal replacement, intubation
44F	Heroin	HT, BP, VD, RD, CNS, MA, AG,	No	No	Naloxone, vasopressors, CPR, intubation, IV fluids
34M	Heroin	RD, CNS	Unknown	Unknown	Naloxone, CPR
26M	Heroin	CNS	Yes	Yes	Naloxone, intubation
70M	Diltiazem	HT, CNS	Yes	Yes	Calcium, insulin-euglycemic therapy, vasopressors, IVF
65M	Opioid unspecified	None listed	No	No	Antihypertensives, opioids,
62F	Ethanol	HT, BC, MI, RD, CNS, MA,AG, OG, GIB, WBC, RBM	No	No	Fomepizole, vasopressors, continuous renal replacement, CPR, intubation, IV fluids
60M	Acetaminophen	None listed	No	No	NAC
32F	Aspirin	HT, BC, VD, RD, CNS,	No	No	$NaHCO_3$, vasopressors, CPR, intubation, IV fluids
32M	Cyanide	RD, CNS, AG, MET	Yes	Yes	Hydroxocobalamin, methylene blue, $NaHCO_3$, vasopressors, intubation, IV fluids

Table 32 (continued)

Age/sex[a]	Agents involved	Clinical findings	Life support withdrawn	Brain death confirmed	Treatment[b]
44M	Acetaminophen	AP, HPT, MET, MYS, CPT, AKI, RBM	Yes	No	NAC, hemodialysis, continuous renal replacement, intubation, IV fluids, transfusion
43M	Methanol	TC, RD, CNS, SZ, MA, AG, OG	Yes	Yes	Folate, fomepizole, thiamine, vasopressors, anticonvulsants, benzodiazepines, hemodialysis, intubation, IV fluids

Based on response from medical toxicologist "Did the patient have a toxicological exposure?" equals yes, with known agent(s)

AG anion gap, *AGT* agitation, *AKI* acute kidney injury, *ALI* acute lung injury/ARDS, *AP* aspiration pneumonia, *AVB* AV block, *BC* bradycardia, *BP* bradypnea, *CNS* coma/CNS depression, *CPT* coagulopathy, *CRV* corrosive injury, *DLM* delirium, *EPS* dystonia/rigidity, *GIB* GI bleeding, *HCN* hallucinations, *HGY* hypoglycemia, *HPT* hepatoxicity, *HT* hypotension, *HTN* hypertension, *HYS* hemolysis, *HYT* hyperthermia, *INT* intestinal ischemia, *MA* metabolic acidosis, *MET* methemoglobinemia, *MI* myocardial injury/ischemia, *NP* neuropathy, *OG* osmole gap, *OTH1* rash, *OTH2* skin blisters, necrosis, *PCT* pancytopenia, *PLT* thrombocytopenia, *PNC* pancreatitis, *PST* paresthesia, *QRS* QRS prolongation, *QTc* QTc prolongation, *RAD* asthma/reactive airway disease, *RBM* rhabdomyolysis, *RD* respiratory depression, *RFX* hyperreflexia/tremor, *SZ* seizures, *TC* tachycardia, *VD* ventricular dysrhythmia, *WBC* leukocytosis, *WKN* weakness/paralysis, *BAL* dimercaprol, *CPR* cardiopulmonary resuscitation, *ECMO* extra-corporeal membrane oxygenation, *NAC* n-acetyl cysteine, $NaHCO_3$ sodium bicarbonate

[a] Age in years unless otherwise stated

[b] Pharmcological and non-pharmacological support as reported by medical toxicologist

Benzodiazepines

Benzodiazepines were again the most commonly reported type of agent in the sedative-hypnotics/muscle relaxants class in 2016. For the first time since the start of the Registry, alprazolam was the most commonly reported benzodiazepine with 276 cases (20.6% of the sedative-hypnotics/muscle relaxants agent class). Clonazepam had previously been the most commonly reported, but was second this year with 207 cases (15.5% of the class). In 2016, the mean age reported for alprazolam ingestions was 33.4 years with 50.7% male. For clonazepam, the mean age reported was 34.5 years with 38.2% males. Lorazepam, the third most common benzodiazepine, had a mean age of 35.3 years in reported cases with 31.3% males. Coingestants were common in benzodiazepine exposures, being reported in 191 (69.2%) alprazolam cases, 165 (79.7%) clonazepam cases, and 76 (76.8%) lorazepam cases. Opioids were commonly reported coingestants for all three benzodiazepines. Eighty-five (30.8%) of alprazolam exposures involved at least one opioid. Cases could involve multiple opioid coingestants. Heroin was the most common opioid reported in alprazolam exposures with 25 cases (9.1%), followed by oxycodone 20 cases (7.2%) and methadone 11 cases (4.0%). Forty-three (20.8%) of the clonazepam exposures involved at least one opioid. As with alprazolam, cases could involve multiple opioid coingestants. Among clonazepam exposures, oxycodone was most commonly reported with 16 cases (7.7%), followed by heroin with 8 cases (3.9%) and hydrocodone with 6 cases (2.9%). Lorazepam exposures involved an opioid in only seven cases (7.1%).

Laundry Detergent Pods

Liquid laundry detergent pods have been responsible for a number of pediatric poisonings, both mild and severe, in the USA and several European countries, with young children (i.e., age 0–6 years) disproportionately affected [14–24]. In response to public concern and warnings from the US Consumer Product Safety Commission (CPSC), the American Association of Poison Control Centers (AAPCC), and others, several manufacturers (including P&G, responsible for 80% of the share of the US market) recently agreed to adopt a new safety standard for detergent pod packaging released in 2015 by the American Society of Testing and Materials [25–28]. Among other things, the standard mandates using opaque instead of clear packaging, adding a bittering agent to the outer membrane, and other features designed to make the pods less attractive to young children [27, 28].

Although it is unclear whether or not these changes have succeeded in reducing accidental pediatric ingestions, the early numbers are promising. Detergent pod cases reported annually to AAPCC/US poison control centers declined in

Table 33 ToxIC 2016 fatality cases with known toxicological exposure, multiple agents

Age/sex[a]	Agents involved	Clinical findings	Life support withdrawn	Brain death confirmed	Treatment[b]
45F	Carbon monoxide, cyanide	HT, TC, ALI, RD, CNS, MA, AG,	Yes	Yes	Hydroxocobalamin, intubation
30M	Heroin, cocaine, diphenhydramine, dextromethorphan, citalopram	TC, AP, CNS, RFX, MA, HPT, CPT, WBC, AKI, RBM, OTH2	Yes	No	$NaHCO_3$, antihypertensives, benzodiazepines, neuromuscular blockers, opioids, hemodialysis, intubation, IV fluids
59M	Acetaminophen, ethanol	HT, RD, CNS, HGY, GIB, CPT	Unknown	Unknown	NAC, intubation, IV fluids
16M	Acetaminophen, ethanol	DLM	Unknown	Unknown	None listed
52F	Nicotine, caffeine, dextromethorphan, venlafaxine	VD, QRS, AP, CNS, GIB	Yes	Yes	NAC, $NaHCO_3$, vasopressors
62M	Heroin, cocaine	HT, BC, QTc, ALI, CNS, MA, AG, HPT, AKI, RBM	Yes	Yes	NAC, naloxone, vasopressors, continuous renal replacement, intubation, IV fluids
68F	Nortriptyline, duloxetine, zolpidem, oxycodone	HTN, HT, TC, AP, ALI, RD, AGT, DLM, RFX, MA, PNC, PLT, AKI, RBM	Yes	No	Naloxone, vasopressors, benzodiazepines, neuromuscular blockers, continuous renal replacement, intubation, IV fluids
Unknown F	Fentanyl, diazepam	HT, RD, CNS, MA	Yes	Yes	Vasopressors, intubation, IV fluids
15F	Ibuprofen, quetiapine	HT, TC, VD, QRS, RAD, CNS, MA, AG,	Yes	Unknown	Insulin-euglycemic therapy, lipid resuscitation, $NaHCO_3$, vasopressors, antiarrhythmics, activated charcoal, hemodialysis, ECMO
32F	Fentanyl, heroin	BC, BP, RD, CNS, SZ, AKI	Yes	No	Naloxone, intubation, IV fluids, therapeutic hypothermia
28M	Methadone, marijuana	CNS, SZ, MA	Unknown	Unknown	Benzodiazepines, neuromuscular blockers, intubation, IV fluids
65F	Hydrocodone, alprazolam, diazepam	HT, RD, CNS	Yes	No	Calcium, glucagon, insulin-euglycemic therapy, NAC, naloxone, vasopressors, intubation, IV fluids
35M	Olanzapine, valproic acid	HT, TC, AGT, DLM	No	No	NAC, $NaHCO_3$, vasopressors, glucose, hemodialysis, intubation, IV fluids
21F	Dextroamphetamine, lithium	AGT, RBM	Unknown	Unknown	IV fluids
33M	Heroin, valproic acid	HT, BC, VD, AP, AP, ALI, RD, CNS	Yes	No	Carnitine, $NaHCO_3$, intubation, IV fluids
50M	Norepinephrine, argatroban	CPT, PLT, WBC, RBM, OTH2	Yes	Unknown	Vasopressors, continuous renal replacement, intubation, IV fluids, transfusion
70M	Warfarin, methadone, oxycodone, cocaine, heroin	HT, RD, CNS, CPT, AKI	Yes	Yes	Vitamin K, vasopressors, IV fluids
57M	Acetaminophen, metformin	HT, BC, RD, CNS, SZ, MA, AG, HPT, PNC, PLT, AKI	No	No	NAC, vasopressors, anticonvulsants, steroids, continuous renal replacement, CPR, intubation
38M	Methamphetamine, amphetamine, marijuana, benzodiazepine	HTN, TC	No	No	Antihypertensives, benzodiazepines, CPR, intubation
54M	Ethanol, ibuprofen, acetaminophen	HT, CNS, MA, AG, HPT, PLT, AKI	No	No	Fomepizole, NAC, vitamin K, vasopressors, hemodialysis, continuous renal replacement, IV fluids
47M	Oxycodone, alprazolam, diazepam	HT, TC, BC, BP, VD, MI, RD, CNS, MA, AKI	Unknown	Unknown	None listed
Unknown M	Cyanide, carbon monoxide	HT, VD, ALI, RD, CNS, AG	Yes	Yes	Hydroxocobalamin, vasopressors, hyperbaric oxygen, intubation, IV fluids
66F	Fentanyl, hydromorphone	BP, RD, CNS, HGY, MA	No	No	Naloxone, glucose, opioids, intubation, IV fluids
77M	Metoprolol, amlodipine	HT, BC, AVB, QRS, ALI, CNS, MA, HPT	Yes	No	

Table 33 (continued)

Age/sex[a]	Agents involved	Clinical findings	Life support withdrawn	Brain death confirmed	Treatment[b]
					Atropine, calcium, glucagon, insulin-euglycemic therapy, vasopressors, glucose, neuromuscular blockers, intubation, IV fluids
53F	Insulin, zolpidem, venlafaxine	AP, CNS	Yes	Yes	Glucagon, naloxone, glucose, intubation, IV fluids
56M	Cocaine, opioid unspecified	MI, AP, RD, CNS, AKI, RBM	Yes	No	Antihypertensives, benzodiazepines, glucose, opioids, intubation, IV fluids
53F	Amlodipine, toluene, doxepin, carisoprodol, clonazepam	HT, BC, VD, QTc, QRS, RD, CNS, RFX, HGY	No	No	Calcium, methylene blue, naloxone, $NaHCO_3$, methylene blue, naloxone, $NaHCO_3$, thiamine, vasopressors, antiarrhythmics, benzodiazepines, glucose, steroids, intubation, IV fluids
41F	Iron, diphenhydramine	HT, TC, BP, VD, ALI, CNS, MA, AG, HPT	No	No	$NaHCO_3$, deferoxamine, vasopressors, hemodialysis, intubation, IV fluids
21F	Hydroxyzine, fluoxetine, melatonin	HT, BP, QTc, RD, CNS, MA, AG, HPT, CPT, AKI, RBM	No	No	NAC, naloxone, vasopressors, CPR, cardioversion, intubation, IV fluids, therapeutic hypothermia
43F	Heroin, cocaine	VD, RD, CNS	Yes	Yes	$NaHCO_3$, vasopressors, intubation, IV fluids
14M	Bupropion, fluoxetine, meclizine	HT, TC, BC, BP, VD, QTc, AP, AGT, CNS, SZ, RFX, MA, RBM	Yes	No	Lipid resuscitation, vasopressors, antiarrhythmics, anticonvulsants, benzodiazepines, neuromuscular blockers, opioids, CPR, ECMO, intubation
57M	Acetaminophen, metformin	HT, CNS, SZ, HGY, MA, AG, HPT, CPT, WBC, AKI, RBM	No	No	NAC, vitamin K, vasopressors, benzodiazepines, steroids, continuous renal replacement, intubation, transfusion
64M	Cyclobenzaprine, gabapentin, acetaminophen, codeine	CNS, AG	Yes	Yes	Naloxone, physostigmine
53M	Metformin, atenolol	HTN, HT, QTc, QRS, MI, MA, AG, HPT, AKI, RBM	No	No	Calcium, lipid resuscitation, $NaHCO_3$, vasopressors, activated charcoal, hemodialysis, intubation, IV fluids

Based on response from medical toxicologist "Did the patient have a toxicological exposure?" equals yes, with known agent(s)

AG anion gap, *AGT* agitation, *AKI* acute kidney injury, *ALI* acute lung injury/ARDS, *AP* aspiration pneumonia, *AVB* AV block, *BC* bradycardia, *BP* bradypnea, *CNS* coma/CNS depression, *CPT* coagulopathy, *CRV* corrosive injury, *DLM* delirium, *EPS* dystonia/rigidity, *GIB* GI bleeding, *HCN* hallucinations, *HGY* hypoglycemia, *HPT* hepatoxicity, *HT* hypotension, *HTN* hypertension, *HYS* hemolysis, *HYT* hyperthermia, *INT* intestinal ischemia, *MA* metabolic acidosis, *MET* methemoglobinemia, *MI* myocardial injury/ischemia, *NP* neuropathy, *OG* osmole gap, *OTH1* rash, *OTH2* skin blisters, necrosis, *PCT* pancytopenia, *PLT* thrombocytopenia, *PNC* pancreatitis, *PST* paresthesia, *QRS* QRS prolongation, *QTc* QTc prolongation, *RAD* asthma/reactive airway disease, *RBM* rhabdomyolysis, *RD* respiratory depression, *RFX* hyperreflexia/tremor, *SZ* seizures, *TC* tachycardia, *VD* ventricular dysrhythmia, *WBC* leukocytosis, *WKN* weakness/paralysis, *BAL* dimercaprol, *CPR* cardiopulmonary resuscitation, *ECMO* extra-corporeal membrane oxygenation, *NAC* n-acetyl cysteine, *$NaHCO_3$* sodium bicarbonate

[a] Age in years unless otherwise stated

[b] Pharmcological and non-pharmacological support as reported by medical toxicologist

Table 34 ToxIC 2016—most common drugs associated with ADRs

	N (%)[a]
Lithium	38 (11.9)
Digoxin	19 (5.9)
Haloperidol	14 (4.4)
Metformin	13 (4.1)
Metoprolol	12 (3.8)
Phenytoin	12 (3.8)
Valproic acid	12 (3.8)
Acetaminophen	9 (2.8)
Olanzapine	9 (2.8)
Sertraline	8 (2.5)

ADRs adverse drug reactions

[a] Percentages are calculated out of the total number of cases reporting an ADR (*N* = 320)

absolute number from 2015 to 2016 (12,616 vs. 11,545 cases, respectively), and monthly case numbers reported in the first half of 2017 were consistently lower than the corresponding months of 2015 and 2016 [26]. Similarly, since the first detergent pod cases were recorded in the ToxIC Registry in 2012, cases involving young children (i.e., age 0–6 years) have declined both in absolute and relative terms, from a peak in 2013 of 32 cases (4.2% of total cases age 0–6 years) to 9 cases (1.4% of total cases age 0–6 years) in 2016 [8, 9]. In 2016, one ToxIC pediatric case involved a 9-year-old female, and all others were age ≤3 years. Among the pediatric cases, central nervous system depression was reported in four, bradypnea with respiratory depression in one, corrosive injury in two, and reactive airway disease and aspiration pneumonitis requiring intubation in one, with no fatalities reported. It is unclear what effect the new safety standards have had on cases of laundry pod exposures as reported to the Registry, though the continued decline is reassuring.

Adverse Drug Reactions

Lithium has been the most commonly reported ADR agent in ToxIC each year since the field was added in 2014 and was responsible for 11.9% of ADRs in 2016 [2, 7]. This is out of proportion to its overall Registry representation, with only 176 total cases involving lithium reported in 2016. Quetiapine was one of the most common medications involved in ADRs in 2014 and 2015 but did not top the list in 2016, despite being the most commonly reported antipsychotic drug in the Registry [2, 7]. Instead, haloperidol and olanzapine were both among the top 10 ADR-related drugs in 2016, together comprising 7.2% of reported ADRs. Digoxin was the second most commonly reported ADR-related drug this year, despite being infrequently reported in the Registry overall; 43.2% of digoxin cases in 2016 were categorized as ADRs. In 2016 acetaminophen was also one of the most common agents associated with an ADR, although ADRs were only implicated in 0.9% of all acetaminophen cases in the Registry. In five ADR cases the outcomes were fatal, with the strength of the association between the exposure and clinical presentation reported as probable in all five. Among those five ADRs which had a fatal outcome, the ages ranged from 41 to 76. Two of the cases were also recorded as medication errors.

Limitations

ToxIC contains data as reported by medical toxicologists treating patients at the bedside, with reliable associations

Table 35 Antidotal therapy administered in ToxIC in 2016

	N (%)[a]
N-Acetylcysteine	974 (27.5)
Naloxone/nalmefene	705 (19.9)
Sodium bicarbonate	421 (11.9)
Thiamine	250 (7.1)
Folate	201 (5.7)
Physostigmine	147 (4.2)
Fomepizole	119 (3.4)
Calcium	110 (3.1)
Glucagon	98 (2.8)
Flumazenil	63 (1.8)
Cyproheptadine	58 (1.6)
Vitamin K	51 (1.4)
Atropine	47 (1.3)
L-Carnitine	44 (1.3)
Insulin-euglycemic therapy	44 (1.3)
Octreotide	44 (1.3)
Fab for digoxin	34 (1.0)
Lipid resuscitation	25 (0.8)
Pyridoxine	26 (0.7)
Hydroxocobalamin	17 (0.5)
Methylene blue	14 (0.4)
Dantrolene	9 (0.3)
2-PAM	7 (0.2)
Bromocriptine	6 (0.2)
Thiosulfate	6 (0.2)
Anticoagulation reversal	5 (0.1)
Botulinum antitoxin	3 (0.1)
Ethanol	2 (0.1)
Nitrites	2 (0.1)
Coagulation factor replacement	1 (<0.1)
Protamine	1 (<0.1)
Total	3540 (100)

[a] Percentages are out of the total number of antidotes administered (*N* = 3540); 3047 cases (35.7% of total Registry cases) received at least one antidote; some cases involve multiple antidotes

Table 36 Antivenom therapy administered in ToxIC in 2016

	N (%)[a]
Crotalidae polyvalent immune fab (ovine)	222 (96.1)
Other snake antivenom	5 (2.2)
Scorpion antivenom	3 (1.3)
Spider antivenom	1 (0.4)
Total	231 (100)

[a] Percentages are out of the total number of antivenom treatments administered (*N* = 231)

between clinical signs and symptoms and the toxic agents responsible. Nonetheless, there are some inherent limitations of the Registry from a descriptive epidemiological perspective, as well as structural and data quality limitations that continue to be addressed through an ongoing quality improvement process. One inherent limitation is that the central case inclusion criterion—consultation by a medical toxicologist—likely creates a reporting bias toward more severe or unusual cases. At the site level, bias may be introduced through either the decision to consult and/or by the reporting medical toxicologist her/himself. We attempt to control this bias through written agreements with the participating sites that every case seen by the medical toxicologist will be logged in the Registry. In addition, ToxIC cases represent those presenting for clinical care, thus are likely biased toward severe/unusual exposures compared to sources such as Poison Control Centers.

Another inherent bias is the limited number of medical toxicologists in practice, currently estimated to be only a few hundred nationwide. This restricts the Registry cases to those geographic areas with actively practicing medical toxicologists, who have also agreed to ToxIC's participation rules and guidelines. Indeed, the Registry has grown to include sites from 22 states across the country and thus includes a large, diverse collection of cases and practice patterns, which for some agents/exposures may reasonably be considered representative of national trends. But some areas, such as the southeastern and western USA, are underrepresented in ToxIC compared to others, so trends unique to those areas may not be fully reflected in the database. Limited case entries required that two of the international sites not be included in the Registry in 2016, thus limiting the scope of data collected largely to the USA.

Table 37 Supportive care interventions administered in ToxIC in 2016—pharmacological

	N (%)[a]
Benzodiazepines	1917 (50.1)
Opioids	415 (10.8)
Vasopressors	393 (10.3)
Antipsychotics	277 (7.2)
Neuromuscular blockers	172 (4.5)
Antihypertensives	160 (4.2)
Anticonvulsants	140 (3.7)
Glucose (concentration > 5%)	134 (3.5)
Corticosteroids	70 (1.8)
Albuterol (or other bronchodilator)	66 (1.7)
Antiarrhythmics	49 (1.3)
Beta blockers	27 (0.7)
Vasodilators	10 (0.3)
Total	3830 (100)

[a] Percentages are out of the total number of treatments administered (3830); 2741 Registry cases (31.8%) received at least one form of pharmacological treatment; cases may have involved multiple forms of treatment

Table 38 Supportive care interventions administered in ToxIC in 2016—non-pharmacological

	N (%)[a]
IV fluid resuscitation	3179 (70.3)
Intubation/ventilatory management	1133 (25.1)
CPR	81 (1.8)
Transfusion	41 (1.0)
Hyperbaric oxygen	19 (0.4)
Cardioversion	18 (0.4)
Therapeutic hypothermia	18 (0.4)
Pacemaker	16 (0.4)
ECMO	11 (0.2)
Aortic balloon pump	1 (0.02)
Organ transplantation	1 (0.02)
Total	4522 (100)

CPR cardiopulmonary resuscitation, *ECMO* extracorporeal membrane oxygenation

[a] Percentages are out of the total number of treatments administered (*N* = 4522); 3508 cases (41.1% of total Registry cases) received at least one form of non-pharmacological treatment; cases may have involved multiple forms of treatment

Table 39 Chelation therapy administered in ToxIC in 2016

	N (%)[a]
Deferoxamine	11 (35.5)
DMSA	11 (35.5)
Dimercaprol	4 (12.9)
EDTA	4 (12.9)
Pencillamine	1 (3.2)
Total	31 (100)

DMSA dimercaptosuccinic acid, *EDTA* ethylenediamine-tetraacetic acid

[a] Percentages are out of the total number of chelation treatments administered (*N* = 31); 28 cases (0.3% of total Registry cases) received at least one form of chelation treatment

Table40 Decontamination interventions administered in ToxIC in 2016

	N (%)[a]
Activated charcoal	265 (79.3)
Whole bowel irrigation	33 (9.9)
External irrigation	29 (8.7)
Gastric lavage	7 (2.1)
Total	334 (100)

[a] Percentages are out of the total number of treatments administered (*N* = 334); 318 cases (3.7% of Registry total) received at least one form of decontamination

In 2014, centralized, ongoing quality assurance procedures were initiated, designed to improve the accuracy of data entry and coding, and to minimize the number of missing entries. Year 2016 is also the second complete year of data collection since several data fields were made mandatory including include race, ethnicity, reason for encounter, presence of suicidal intent, signs and symptoms, treatments, other interventions, and fatalities. Prior to this, it was unknown if items left blank were not applicable or simply not recorded. This improvement has nearly eliminated missing responses in these fields, and future research will benefit from the improved clarity of responses.

Despite the fact that the race and ethnicity questions were made mandatory in 2014, approximately one quarter of cases were reported as unknown/uncertain race and/or ethnicity in both 2015 and 2016. These data are not self-reported and may not routinely be reflected in patient charts, requiring the examiner to specifically recall this information. For some participating clinicians, race and ethnicity may not be a routine part of their information gathering. Additionally, with the Registry's potential bias toward more complicated and critically ill exposures, there may be a larger than expected number of patients unable to report this information to the examiner. Quality improvement efforts continue, with a goal of minimizing the number of cases reported as unknown or uncertain race and ethnicity.

Significant physical examination findings, vital sign abnormalities, supportive interventions, and some clinical laboratory data are collected; however, the severity of illness is not directly recorded. Although the completeness of the clinical data has improved since creating the mandatory fields, there remain some cases, such as fatalities, where multiple interventions might be expected but are not recorded. In addition, the timeline of events and cause of death are not described. Multiple agents may be reported, but unless free text fields are used, it may be unclear to what degree each agent contributed.

Additional limitations include those inherent in any database. Each case is unique, and some details may be too complicated to be adequately described in a series of programmed data fields. Free text fields are available to enter additional information at the medical toxicologist's discretion, but the free text fields are not easily searchable and must be reviewed manually.

Table 41 Enhanced elimination interventions administered in ToxIC in 2016

	N (%)[a]
Hemodialysis (toxin removal)	103 (32.1)
Urinary alkalinization	94 (29.3)
Hemodialysis (other indication)	61 (19.0)
Continuous renal replacement therapy	55 (17.1)
Multiple-dose activated charcoal	6 (1.9)
Exchange Transfusion	2 (0.6)
Total	321 (100)

[a] Percentages are out of the total number of treatments administered (*N* = 321); 280 cases (3.3% of total Registry cases) received at least one form of enhanced elimination

Conclusions

Since its inception in 2010, the ToxIC Registry has continued to grow and is the only database of its kind logging all cases encountered by participating medical toxicologists. While agent frequencies may vary from year to year, and new trends may emerge, overall the most common exposures, toxidromes, clinical abnormalities, and antidotes recorded in ToxIC represent the routine practice of the subspecialty of medical toxicology. It is thus potentially useful as an instructional tool for trainees in toxicology, valuable for toxicosurveillance and research, and as a resource for the practice of medical toxicologists.

Acknowledgments Toxicology Investigators Consortium (ToxIC) Study Group Collaborators:

Aks SE, Algren DA, Alwasiyah D, Beauchamp G, Bentur Y, Beuhler MC, Boyle KL, Bruccoleri RE, Burns, MM, Cahana A, Cannon RD, Caravati EM, Carey JL, Chhabra N, Chomin J, Christian MR, Conner K, Cook MD, Cumpston KL, Dissanayake V, Dribben WH, Eisenga BH, Engebretsen KM, Falkowitz D, Farkas A, Fenton A, Froberg BA, Furmaga JF, Ganetsky M, Garlich F, Geib AJ, Gorodetsky R, Greene S, Greller HA, Gummin DD, Hart K, Hendrickson RG, Hernandez S, Hoyte CO, Judge BS, Kazzi Z, Kerns W, Kessler BD, King J, Kirschner R, Kleinschmidt KC, Kostic MA, Kusin S, Leikin, JB,LeRoy JM, Levine M, Lo CY, Lowry JA, Lung D, Lurie Y, Maddry J, Majlesi N, Manini AF, Marlin MB, McKay C, McKeever RG, McKeown NJ, Meggs WJ, Miller SN, Minns A, Moore E, Morgan BW, Mullins ME, Nappe TM, Nogar JN, Oakley E, Olmedo R, Othong R, Parker-Cote J,Regina A, Riley BD, Rowden A, Ruha AM, Rusyniak DE, Schult, R, Schwarz ES, Seifert SA, Sessions D, Shulman J, Smolinske SC, Smollin C, Spyres MB, Steck A, Stellpflug SJ, Sullivan R, Toce MS, Troendle MM, Vearrier D, Warrick BJ, Watts DC, Wills BK, Wolk BJ, Zosel AE.

We also wish to thank study coordinators AB Adefeso, Mary Connie Aubin, Anita Kurt, Julie Licata, Misti Marshall, Maureen Morgan, Tammy Phan, Andrea Ramirez, and Melissa VandenBerg.

Compliance with Ethical Standards

Funding ToxIC was supported by a continuation of a grant from the US National Institutes of Health on cardiovascular drug toxicity, a new contract with the US Food and Drug Administration, and the continuation of unrestricted grant support from BTG International, which was used to support the North American Snakebite Registry.

Conflicts of Interest None

Previous Presentation of Data None

Funding Sources This study received funding from the NIH National Institute on Drug Abuse 1R56DA38366, and 1R01DA037317-01, a data sharing contract with the U.S. Food and Drug Administration, and BTG International Inc.

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