Journal of Medical Toxicology
https://doi.org/10.1007/s13181-023-00962-2

ORIGINAL ARTICLE

The Toxicology Investigators Consortium 2022 Annual Report

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Received: 9 July 2023 / Revised: 31 July 2023 / Accepted: 2 August 2023
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Abstract

Since 2010, medical toxicology physicians from the American College of Medical Toxicology (ACMT) Toxicology Investigators Consortium (ToxIC) have provided reports on their in-hospital and clinic patient consultations to a national case registry, known as the ToxIC Core Registry. De-identified patient data entered into the registry includes patient demographics, reason for medical toxicology evaluation, exposure agents, clinical signs and symptoms, treatments and antidotes administered, and mortality. This thirteenth annual report provides data from 7206 patients entered into the Core Registry in 2022 by 35 participating sites comprising 52 distinct healthcare facilities, bringing the total case count to 94,939. Opioid analgesics were the most commonly reported exposure agent class (15.9%), followed by ethanol (14.9%), non-opioid analgesic (12.8%), and antidepressants (8.0%). Opioids were the leading agent of exposure for the first time in 2022 since the Core Registry started. There were 118 fatalities (case fatality rate of 1.6%). Additional descriptive analyses in this annual report were conducted to describe the location of the patient during hospitalization, telemedicine consultations, and addiction medicine treatments.

Keywords Poisoning · Overdose · Surveillance · Epidemiology · Medical Toxicology

Introduction

The Toxicology Investigators Consortium (ToxIC) Core Registry was established by the American College of Medical Toxicology (ACMT) in 2010. ToxIC's initial project was a case registry of patients seen by medical toxicology physicians through consultations conducted at the bedside and in the clinic [1–12]. Known as the ToxIC Core Registry, patient accrual into this registry has been ongoing since 2010 [1, 2]. The main objectives of the ToxIC Core Registry are to describe toxicological exposures seen by medical toxicology physicians and to provide a data source for research in medical toxicology. Each year, an annual report summarizing this data has been published. This thirteenth annual report provides data from 7206 patients entered into the Core Registry in 2022 by 35 participating sites comprising 52 distinct healthcare facilities.

Within the Core Registry, more detailed data on specific patient populations are gathered through sub-registries and/

Supervising Editor: Mark B. Mycyk, MD

Previous presentation of data Data in this manuscript were previously presented at ACMT's Annual Scientific Meeting, San Diego, California 2023.

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Published online: 29 August 2023

or focused data collection. The North American Snakebite Registry (NASBR) is one of the largest sub-registries and includes patients with snakebites who have been treated by medical toxicology physicians (Principal Investigator (PI): Anne-Michelle Ruha, MD; funded by BTG Pharmaceuticals, a SERB company). NASBR has accrued more than 1,800 cases since 2013, with detailed data on circumstances of snakebite, clinical manifestations, and response to treatment. NASBR investigators published research in 2022 on late hemotoxicity among snakebite patients treated with crotalidae immune F(ab')2 (equine) antivenom and crotalidae immune polyvalent Fab (ovine) antivenom [13].

The Novel Opioid and Stimulant Exposures (NOSE) focused data collection (PI: Meghan Spyres, MD; funded by SAMHSA 1H79TI085588) provides comprehensive case narratives on patients evaluated by medical toxicology physicians who may have been exposed to a novel agent or had an unusual presentation to a common agent. Coordinated by the American Academy of Addiction Psychiatry (AAAP), quarterly reports on findings are disseminated through the Opioid Response Network (ORN). ToxIC NOSE briefs in 2022 included topics on xylazine, wound botulism, and illicit fentanyl.

Two additional ongoing sub-registries include the Natural Toxins Registry: Mushrooms and Plants, and the Extracorporeal Therapies Registry.

Other ToxIC Multicenter Projects

Since 2020 ToxIC has initiated several multicenter projects separate from the ToxIC Core Registry and Sub-registries. These individual projects leverage the ToxIC infrastructure with medical toxicology physicians serving as PIs at each site.

The Fentalog Study is an ongoing, 5-year prospective cohort study (PI: Alex Manini; NIH NIDA 5R01DA048009 and CDC Supplement R01DA048009-03S1). This study, titled "Predicting Medical Consequences of Novel Fentanyl Analog Overdose Using the Toxicology Investigators Consortium (ToxIC)", enrolls patients who have a suspected opioid overdose who present to the emergency department at one of 10 participating medical centers. Patient demographics, comorbidities, clinical treatments, and outcome data are collected through chart reviews. Waste blood samples collected for routine laboratories are obtained and sent to the Center for Forensic Science Research and Education (CFSRE) for qualitative toxicology analyses to determine the presence of over 1,000 novel psychoactive substances, illicit substances (e.g., fentanyl, fentanyl analogs, and illicit benzodiazepines), and adulterants (e.g., xylazine) [14]. From 2020–2022, 921 cases were enrolled. The first reported human exposure to N-piperidinyl etonitazene found in 3 patients from one study site was published in 2022 [15].

In 2020, the Food and Drug Administration (FDA) ACMT COVID-19 ToxIC (FACT) Pharmacovigilance Project (FDA #75F40119D10031) was initiated in response to the COVID-19 pandemic. The project implemented a real-time national toxico-surveillance reporting program at 15 ToxIC sites that identified adverse events associated with COVID-19 therapeutics. By the end of 2022, the project had expanded to 17 sites and 1263 cases with suspected adverse events had been reported, including adverse events to ivermectin [16].

ToxIC Publications and Presentations

Nine peer-reviewed ToxIC publications were released in 2022. In addition, 25 ToxIC abstracts were presented at the North American Congress of Clinical Toxicology (NACCT) meeting, ACMT Annual Scientific Meeting (ASM), and European Association of Poison Centers and Clinical Toxicologists (EAPCCT) meeting. These publications and abstracts are detailed on the ToxIC website: www.toxicregistry.org.

Changes to the ToxIC Core Registry in 2022

As the ToxIC Core Registry continues to grow, changes are made each year to augment data collection. In 2022, new sections were added on past medical history, past psychiatric history, and current and past misuse of pharmaceutical and non-pharmaceutical agents. A new question about the locations of the patient during hospitalization (e.g.,critical care unit, hospital floor, emergency department only) was added as a representation of hospital resource utilization and exposure severity.

Annual Report Objectives

The objective of this annual report is to describe the cases entered into the ToxIC Core Registry in 2022. In addition to a summary of the Core Registry data, descriptive analyses were conducted to describe the location of the patient during hospitalization, telemedicine consultations, and addiction medicine treatments.

Methods

Medical toxicology physicians at participating healthcare sites within the ToxIC Core Registry enter deidentified patient information from medical toxicology consultations and evaluations at the bedside, in the clinic, and via telemedicine. Study data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at Vanderbilt University [17, 18].

REDCap is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources.

The data gathered in the Core Registry by medical toxicology physicians is a culmination of information from the patient's electronic medical record and their first-hand evaluation of the patient during their consultation utilizing available evidence (e.g., patient self-report or family report, presence of the product of exposure, clinical presentation, physical examination, ancillary data, and/or laboratory testing results). Figure 1 contains a brief overview of the Core Registry data collection elements.

All cases entered into the Core Registry and associated sub-registries/focused data collections are reviewed for quality assurance (QA) by the ToxIC staff. Any inconsistent or incomplete entries are queried back to the entering medical toxicologist for correction or clarification. ToxIC leadership and staff communicate with all sites to review patient accrual, barriers to data entry, quality assurance efforts, and ongoing project opportunities. Additional information regarding ToxIC can be found at www.toxicregistry.org.

Each ToxIC project has been reviewed by the WCG Institutional Review Board (WCG IRB) and operates in accordance with the approval of the participating site IRBs. All data collected by ToxIC is deidentified and compliant with the Health Insurance Portability and Accountability Act (HIPAA).

Statistical Analysis

Data from January 1, 2022-December 31, 2022 were extracted from REDCap and exported into Microsoft Excel. Descriptive statistics were calculated to obtain relative and absolute frequencies for demographics, advanced demographics, past history, medical toxicology consultation location, exposure and treatment information, and mortality among cases in the ToxIC Core Registry. Small cell sizes for specific agent exposures were collapsed into "miscellaneous" categories which are detailed in footnotes for relevant tables.

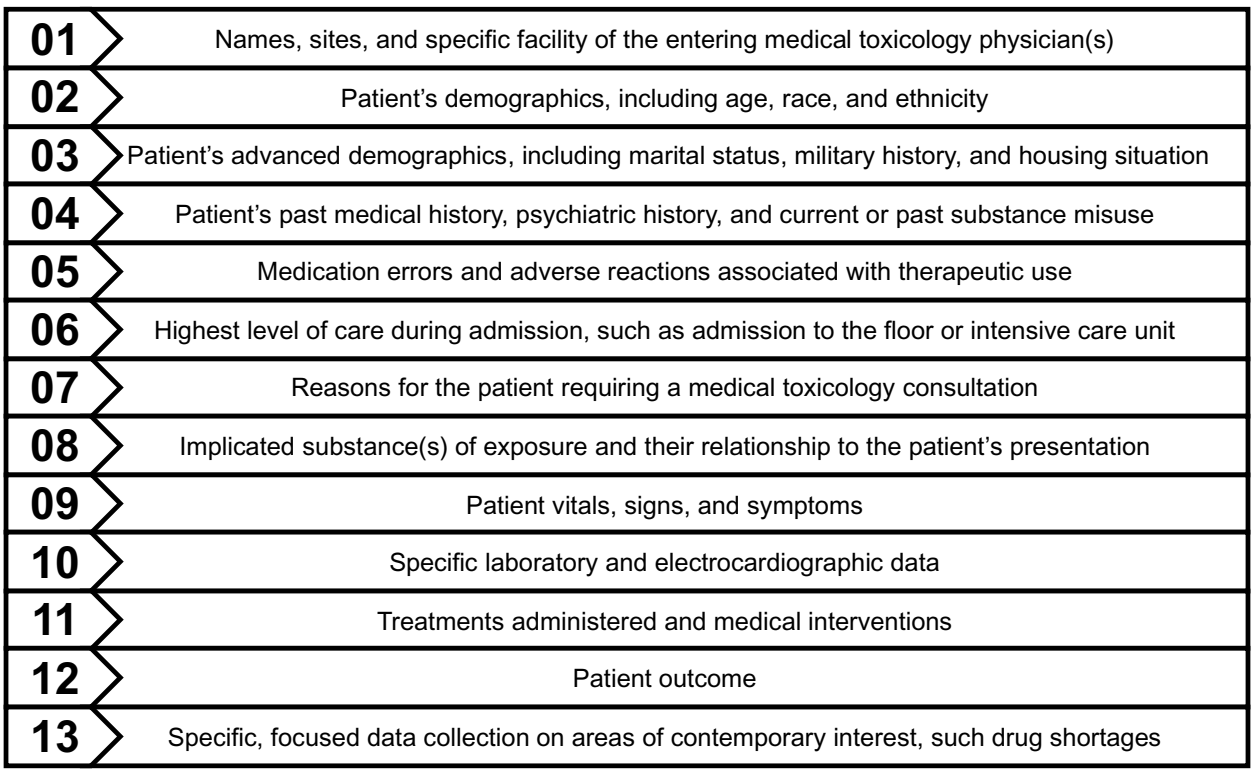

Fig. 1 Core Registry data collection elements.

Table 1 Participating institutions providing cases to ToxIC in 2022.

State or Country	City	Hospitals
Arizona	Phoenix	Banner—University Medical Center Phoenix
		Phoenix Children's Hospital
Alabama	Birmingham	University of Alabama at Birmingham Hospital
Arkansas	Little Rock	Arkansas Children's Hospital
California	Loma Linda	Loma Linda University Medical Center
	Los Angeles	University of California Los Angeles—Olive View
		University of California Los Angeles—Ronald Reagan
		University of California Los Angeles—Santa Monica
	Sacramento	University of California Davis Medical Center
Colorado	Denver	Colorado Children's Hospital
		Denver Health Medical Center
		Porter and Littleton Hospital
		Swedish Hospital
		University of Colorado Hospital
Connecticut	Hartford	Hartford Hospital
Florida	Jacksonville	University of Florida Health Jacksonville
Georgia	Atlanta	Grady Memorial Hospital
Indiana	Indianapolis	Indiana University—Eskenazi Hospital
		Indiana University—Indiana University Hospital
		Indiana University—Methodist Hospital-Indianapolis
		Indiana University—Riley Hospital for Children
Kansas	Kansas City	University of Kansas Medical Center
Kentucky	Lexington	University of Kentucky Chandler Medical Center
		University of Kentucky Good Samaritan Hospital
Massachusetts	Boston	Boston Children's Hospital
	Worcester	University of Massachusetts Memorial Medical Center
Michigan	Grand Rapids	Corewell Health (previously Spectrum Health Hospitals)
Mississippi	Jackson	University of Mississippi Medical Center
Missouri	Kansas City	Children's Mercy Hospitals & Clinics
	St. Louis	Missouri Baptist Medical Center
		Washington University School of Medicine in St. Louis
Nebraska	Omaha	University of Nebraska Medical Center
New Jersey	Newark	Rutgers/New Jersey Medical School
New York	Rochester	Strong Memorial Hospital
	Syracuse	Upstate Medical University—Downtown Campus
North Carolina	Charlotte	Carolinas Medical Center
Oregon	Portland	Doernbecher Children's Hospital
		Oregon Health & Science University Hospital
Pennsylvania	Bethlehem	Lehigh Valley Hospital—Cedar Crest
		Lehigh Valley Hospital—Muhlenberg
	Philadelphia	Einstein Medical Center Philadelphia*
	York	York Hospital
Texas	Dallas	Children's Medical Center Dallas
		Parkland Memorial Hospital
		William P. Clements Jr University Hospital
	Houston	HCA Houston Healthcare Kingwood
Virginia	Charlottesville	University of Virginia Health
Canada	Calgary	Foothills Medical Centre
England	London	Guy's and St Thomas' NHS Foundation Trust
		St Thomas' Hospital
Israel	Haifa	Rambam Health Care Campus
Thailand	Bangkok	Vajira Hospital

*New participating ToxIC sites in 2022

Table 2 Patient gender and pregnancy status.

	N (%)
Female	3437 (47.7)
Male	3690 (51.2)
Transgender	79 (1.1)
Female to male[a]	40 (50.6)
Gender non-conforming[a]	21 (26.6)
Male to female[a]	17 (21.5)
Missing[a]	1 (1.3)
Total	7206 (100)
Pregnant[b]	119 (3.5)

[a] Percentages based on total number of transgender cases ($N=79$)

[b] Percentage based on number of cases in female patients ($N=3437$)

Results

In 2022, there were a total of 7206 cases of toxicologic exposures reported to the ToxIC Core Registry from 52 healthcare facilities at 35 sites. Individual facilities contributing cases in 2022 are listed in Table 1. One new site, Einstein Medical Center Philadelphia, initiated data collection in 2022.

Demographics

In 2022, 47.7% of cases involved female patients, and 1.1% of patients identified as transgender or as gender non-conforming (50.6% female-to-male, 21.5% male-to-female and 26.6% as gender non-conforming). Among female patients, the pregnancy prevalence was 3.5% (Table 2).

The most prevalent age group was adults 19–65 years old (61.9%). Adolescents ages 13–18 comprised 19.3% of cases, 10.4% of cases were children ≤ 12 years of age, and 8.2% of cases were older adults > 65 years old (Table 3).

Table 4 details patient race/ethnicity. Patients were primarily Non-Hispanic White (63.7%), followed by Black/African American (15.4%) and Hispanic (13.3%).

Table 3 Patient age category.

	N (%)
Less than 2 years old	211 (2.9)
2–6 years old	299 (4.1)
7–12 years old	244 (3.4)
13–18 years old	1390 (19.3)
19–65 years old	4458 (61.9)
66–89 years old	583 (8.1)
Over 89 years old	10 (0.1)
Age unknown	11 (0.2)
Total	7206 (100)

Table 4 Patient race/ethnicity.

	N (%)
American Indian/Alaskan Native	121 (1.7)
Asian	154 (2.1)
Black/African American	1113 (15.4)
Non-Hispanic White	4588 (63.7)
Hispanic	962 (13.3)
Mixed, not otherwise specified	44 (0.6)
Native Hawaiian/Pacific Islander	12 (0.2)
Race Other	6 (0.1)
Race unknown	206 (2.9)
Total	7206 (100)

Advanced Demographic Characteristics

Marital status and military service are reported for patients > 12 years of age (Table 5). The majority of patients reported being single (68.4%) followed by married or with a long-term partner (19.8%) and widowed (2.6%). Of the 41.5% with military status documented, the majority of patients (97.6%) reported no prior military service. Of the 2.4% who reported prior military service, 84.6% were retired or had former military service.

Among patients with housing status information (92.0%), most patients (92.7%) reported a secure or stable living situation and 5.9% reported being undomiciled, where they were experiencing homelessness or an unstable living situation.

Source of Medical Toxicology Referral and Location of Patient Consultation Encounter

Table 6 details the sources of medical toxicology physician consultation referral for inpatient and outpatient encounters. In-hospital consultations primarily consisted of referrals from the Emergency Department (55.5%) or admitting service (33.4%). Few consultations were poison center referrals (0.8%) or primary care/outpatient physician referrals (0.1%). The majority of outpatient consultations in a clinic or office were referred by a primary care or other outpatient physician (59.7%) followed by patient self-referrals (24.3%).

All patient locations at the time of the medical toxicology consultation are reported in Table 7. Patients could be initially evaluated in one location and have follow-up evaluations in another location. Therefore, patients could be seen in more than one location by the medical toxicology physician throughout their hospitalization. For example, if a patient was seen by a medical toxicology physician in the emergency department and then also seen by the medical toxicology physician on the hospital floor, the patient would have two locations for medical toxicology encounters. The majority of patients were seen by a toxicology physician in

Table 5 Patient marital status, military service, and housing situation.

	N (%)
Marital Status	
Unknown[a]	961 (14.9)
Total reported marital status[a]	5491 (85.1)
Single[b]	3757 (68.4)
Married or long-term partner[b]	1090 (19.8)
Divorced or separated[b]	503 (9.2)
Widowed[b]	141 (2.6)
Military Service	
Unknown[a]	3774 (58.5)
Total reported military service[a]	2678 (41.5)
No, previous military service[c]	2613 (97.6)
Yes, previous military service[c]	65 (2.4)
Former/retired[d]	55 (84.6)
Current (including reserves)[d]	5 (7.7)
Unknown if former/current[d]	5 (7.7)
Housing Status	
Unknowne	575 (8.0)
Total reported housing status[e]	6631 (92.0)
Secured housing (home or stable living situation)[f]	6150 (92.7)
Undomiciled (homelessness, unsecured housing)[f]	388 (5.9)
Non-criminal supervised care (foster, group home, nursing home)[f]	25 (0.4)
Rehabilitation or psychiatric facility[f]	21 (0.3)
Correctional related facility (jail, prison, incarceration)[f]	39 (0.6)
Other[f]	8 (0.1)

[a] Percentages based on patients age > 12 years old ($N=6452$)

[b] Percentages based on total cases reporting marital status ($N=5491$)

[c] Percentages based on total cases reporting military service ($N=2678$)

[d] Percentages based on total cases reporting yes, previous military service ($N=65$)

[e] Percentages based on total reported cases ($N=7206$)

[f] Percentages based on total cases reporting housing status ($N=6631$)

the Emergency Department (49.9%) while 23.1% were seen in the intensive care unit (ICU)/neonatal ICU (NICU).

Table 8 describes *all* locations of the patient during hospitalization. Most patients spent time in the Emergency Department (76.9%), hospital floor (60.2%), and critical care units (28.2%). Each patient may have more than one hospital location during their hospitalization.

Telemedicine referrals (Table 9) were primarily from the Emergency Department (42.5%) and admitting service (42.0%), followed by primary care provider or other outpatient treating physician (11.1%) and then by request from another hospital service outside of the emergency department (3.9%). The most common telemedicine encounters were conducted via video/internet (53.1%) and chart review only (44.0%). Only 2.9% were conducted over the phone. The top four reasons for telemedicine encounters included attempt at self-harm (26.6%), ethanol and/or alcohol withdrawal (17.3%), misuse/abuse (12.1%), and addiction medicine (10.6%).

Table 10 describes the primary reason for the medical toxicology encounter. Similar to past years, intentional pharmaceutical exposures were the most common reason for medical toxicology encounters (32.0%). Among intentional pharmaceutical exposures (Table 11), most cases were attempts at self-harm (73.6%), and 12.7% were classified as misuse/abuse. Among the patients with reported self-harm attempts, the majority of these attempts were classified as suicidal intent (82.2%) and 3.9% were classified as no suicidal intent. The remaining patients (13.7%) had unknown suicidal intent.

Table 12 describes addiction medicine consultations reported in 2022. Addiction medicine consults accounted for 7.3% of all medical toxicology encounters. The majority of consultations were for opioid agonist therapy (68.7%) followed by counseling and support (14.2%) and pain management (8.7%).

Table 6 Case referral sources by inpatient/ outpatient status.

	N (%)
Emergency Department (ED) or Inpatient (IP)[a]	
ED	3917 (55.5)
Admitting service	2358 (33.4)
Request from another hospital service (not ED)	448 (6.3)
Outside hospital transfer	271 (3.8)
Poison Center	56 (0.8)
Primary care provider or other outpatient treating physician	5 (0.1)
Self-referral	5 (0.1)
Employer/Independent medical evaluation	2 (0.0)
Total	7062 (100)
Outpatient (OP)/Clinic/Office Consultation[b]	
Primary care provider or other OP physician	86 (59.7)
Self-referral	35 (24.3)
Employer/Independent medical evaluation	14 (9.7)
Admitting service	3 (2.1)
ED	3 (2.1)
Request from another hospital service (not ED)	2 (1.4)
Outside hospital transfer	1 (0.7)
Poison Center	0 (0.0)
Total	144 (100)

[a] Percentages based on total number of cases ($N=7062$) seen by a medical toxicologist as consultant (ED or IP) or as attending (IP)

[b] Percentages based on total number of cases ($N=144$) seen by a medical toxicologist as outpatient, clinic visit, or office consultation

Table 7 Locations of medical toxicology encounters during hospitalization.

	N (%)[a]
ED	3524 (49.9)
Hospital floor	2971 (42.1)
ICU/NICU	1628 (23.1)
Observation unit	136 (1.9)

[a] Percentages based on total number of cases ($N=7062$) seen by a medical toxicologist as consultant (ED or IP) or as attending (IP). Case numbers may include more than one hospital location for medical toxicology encounters. Only one unique case is represented within each location

Table 8 Locations of patient during hospitalization.

	N (%)[a]
ED	5433 (76.9)
Hospital floor	4253 (60.2)
Critical care unit	1989 (28.2)
Observation unit	214 (3.0)
Inpatient psychiatric unit	192 (2.7)

[a] Percentages based on total number of cases ($N=7062$) seen by a medical toxicologist as consultant (ED or IP) or as attending (IP). Case numbers may include more than one hospital location. Only one unique case is represented within each location

Agent Classes

Patient toxicologic exposure by agent class reported during the medical toxicology consultation are described in Table 13. The total number of agent classes reported was 9310. Of the 7206 cases entered into the Core Registry in 2022, 6456 included at least one specific agent of exposure. Single agents were involved in 4662 (72.2%) cases. The top three most prevalent exposure classes were opioids (15.9%), ethanol (14.9%), and analgesics (12.8%).

Opioids

Opioid agents are listed in Table 14. Fentanyl was the most commonly reported opioid agent in 2022 (53.9%), while the proportion of heroin cases within the opioid agent class was only 9.4%. Oxycodone (8.1%), methadone (7.0%), and unspecified opioids (6.8%) were the next most frequently reported agents.

Table 9 Telemedicine encounters.

	N (%)[a]
Source of Telemedicine Referral	
ED	88 (42.5)
Admitting service	87 (42.0)
Primary care provider or other outpatient treating physician	23 (11.1)
Request from another hospital service (not ED)	8 (3.9)
Self-referral	1 (0.5)
Nature of Telemedicine Consultation	
Patient encounter via video/internet	110 (53.1)
Chart review only	91 (44.0)
Patient encounter over the phone	6 (2.9)
Reason for Telemedicine Encounter	
Attempt at self-harm[b]	55 (26.6)
Misuse/abuse[b]	25 (12.1)
Addiction medicine consult[c]	22 (10.6)
Withdrawal – Ethanol	21 (10.1)
Withdrawal – opioids	19 (9.2)
Environmental evaluation	18 (8.7)
Unintentional pharmaceutical and/or nonpharmaceutical exposures	17 (8.2)
Ethanol abuse	15 (7.2)
Interpretation of laboratory data	7 (3.4)
Miscellaneous[d]	16 (7.2)
Total Telemedicine Encounters	207 (100)

[a] Percentages based on total cases indicating a telemedicine consultation ($N=207$)

[b] Includes intentional pharmaceutical and/or intentional nonpharmaceutical exposures

[c] Includes opioid agonist therapy, opioid antagonist therapy, pain management, and alcohol dependency pharmacotherapy

[d] Includes envenomation (snake), occupational evaluation, organ system dysfunction, withdrawal (sedative), and withdrawal (other)

Ethanol and Toxic Alcohols

Ethanol was considered its own agent class separate from non-ethanol toxic alcohols (Table 15). The most commonly reported non-ethanol alcohols and glycols were isopropanol (40.0%), ethylene glycol (18.3%) and methanol (18.3%).

Analgesics

Among the non-opioid analgesic class, acetaminophen was the most prevalent agent (67.3%) (Table 16). Ibuprofen was the next most commonly reported agent (13.1%), followed by gabapentin (6.2%). Aspirin and acetylsalicylic acid are listed as separate agents in the Core Registry, but when combined they made up 7.9% of the agent class.

Antidepressants

Table 17 describes the antidepressant class agents. Selective serotonin reuptake inhibitors (SSRIs) (43.9%) and other antidepressants (38.9%) represented the majority of agents. Sertraline (16.0%) was the most common SSRI reported. The other antidepressant category consisted of bupropion (24.5%), trazodone (10.6%), mirtazapine (3.2%), and other miscellaneous antidepressants (0.6%). Tricyclic antidepressants were reported in 8.0% of cases.

Sympathomimetics

Table 18 presents the sympathomimetic class. The three most common agents in 2022 were methamphetamine (42.4%), cocaine (30.2%), and amphetamine (8.8%).

Sedative Hypnotics/Muscle Relaxants

Benzodiazepines (Table 19) represented the majority (63.2%) of the sedative-hypnotic/muscle relaxant class, followed by muscle relaxants (20.6%), other sedatives (9.0%), non-benzodiazepine agonists (5.4%), and barbiturates (1.8%). The benzodiazepines alprazolam (22.9%) and clonazepam

Table 10 Reason for medical toxicology encounter.

	N (%)[a]
Intentional exposure—pharmaceutical	2654 (32.0)
Withdrawal—ethanol	1010 (12.2)
Ethanol abuse	806 (9.7)
Intentional exposure—non-pharmaceutical	723 (8.7)
Withdrawal—opioid	635 (7.7)
Addiction medicine consultation	527 (6.4)
Unintentional exposure—pharmaceutical	493 (5.9)
Organ system dysfunction	341 (4.1)
Unintentional exposure—non-pharmaceutical	328 (4.0)
Envenomation—snake	268 (3.2)
Interpretation of toxicology lab data	188 (2.3)
Environmental evaluation	127 (1.5)
Withdrawal—sedative/hypnotic	77 (0.9)
Envenomation—spider	33 (0.4)
Withdrawal—cocaine/amphetamine	29 (0.3)
Occupational evaluation	21 (0.3)
Withdrawal—other	15 (0.2)
Malicious/criminal	9 (0.1)
Envenomation—other	8 (0.1)
Envenomation—scorpion	4 (0.0)
Marine /fish poisoning	0 (0.0)
Total	8296 (100)

[a] Percentages based on total number of reasons for toxicology encounter ($N=8296$). Case entries may include more than one reason for a medical toxicology encounter

Table 11 Detailed reason for encounter—intentional pharmaceutical exposure[a].

	N (%)
Reason for Intentional Pharmaceutical Exposure Subgroup[b]	
Attempt at self-harm	1948 (73.6)
Misuse/abuse	337 (12.7)
Therapeutic use	230 (8.7)
Unknown	137 (5.2)
Attempt at Self-harm—Suicidal Intent Subclassification[c]	
Suicidal intent	1602 (82.2)
Suicidal intent unknown	266 (13.7)
No suicidal intent	75 (3.9)

[a] Eight cases listed more than one reason for encounter due to intentional pharmaceutical exposure

[b] Percentage based on number of cases reporting intentional pharmaceutical exposure ($N=2646$)

[c] Percentage based on number of cases indicating attempt at self-harm ($N=1948$)

(14.6%) were the most common individual agents overall, followed by the muscle relaxant baclofen (8.5%).

Table 12 Addiction medicine consultations.

	N (%)[a]
Opioid agonist therapy	362 (68.7)
Counseling and support only	75 (14.2)
Pain management	46 (8.7)
Alcohol dependence pharmacotherapy	34 (6.5)
Opioid antagonist therapy	10 (1.9)
Total	527 (100)

[a] Percentage based on total number indicating addiction medicine consultations ($N=527$)

Anticholinergic/Antihistamine

Table 20 describes the anticholinergic/antihistamine class specific agent exposures. Diphenhydramine (56.3%) and hydroxyzine (21.2%) were the most prevalent reported agents in this class.

Cardiovascular Agents

Among cardiovascular agents, sympatholytic alpha-2-agonists (29.5%) remain the most common subclass (Table 21). This was followed by beta blockers (26.3%) and calcium channel blockers (16.1%). Among the cardiovascular agents, clonidine (21.3%), amlodipine (10.9%), and propranolol (10.2%) were the most common individual agents reported.

Psychoactives

The psychoactive classes include psychoactives such as cannabis, ketamine, and lysergic acid diethylamide (LSD) (Table 22). Among the psychoactive agents, cannabis (32.2%) was the most prevalent agent in this class, followed by tetrahydrocannabinol (31.1%). Synthetic cannabinoid cases comprised 4.0% of other psychoactive agents.

Antipsychotics

Quetiapine (40.5%) was the most commonly reported antipsychotic agent, followed by aripiprazole (14.3%) and olanzapine (13.7%) (Table 23).

Envenomations

Table 24 shows data on envenomations and marine poisonings; however, no marine envenomations were reported in 2022. Snakes were the most prevalent type of envenomation (87.6%). Among snake envenomations, *Agkistrodon* (44.7%) and *Crotalus* (38.0%) were most frequently reported. *Loxosceles* spider exposures were reported in 6.9% of all envenomations.

Table 13 Exposure agent classes reported in medical toxicology consultations.

	N (%)[a]
Opioid	1483 (15.9)
Ethanol	1384 (14.9)
Analgesic	1190 (12.8)
Antidepressant	838 (9.0)
Sympathomimetic	746 (8.0)
Sedative-hypnotic/muscle relaxant	554 (6.0)
Anticholinergic/antihistamine	487 (5.2)
Cardiovascular	460 (4.9)
Psychoactive	354 (3.8)
Antipsychotic	321 (3.4)
Envenomation	291 (3.1)
Anticonvulsant	173 (1.9)
Gases/irritants/vapors/dusts	118 (1.3)
Diabetic medication	101 (1.1)
Metals	99 (1.1)
Lithium	83 (0.9)
Herbal products/dietary supplements	70 (0.8)
Toxic alcohols	60 (0.6)
Cough and cold products	60 (0.6)
Antimicrobials	44 (0.5)
Other pharmaceutical product	41 (0.4)
Caustic	40 (0.4)
Plants and fungi	40 (0.4)
Unknown class	38 (0.4)
Household products	36 (0.4)
Chemotherapeutic and immune	24 (0.3)
Gastrointestinal	24 (0.3)
Hydrocarbon	24 (0.3)
Anesthetic	21 (0.2)
Endocrine	20 (0.2)
Other nonpharmaceutical product	20 (0.2)
Anticoagulant	19 (0.2)
Insecticide	16 (0.2)
Ingested foreign body	7 (0.1)
Amphetamine-like hallucinogen	5 (0.1)
Anti-parkinsonism drugs	5 (0.1)
Pulmonary	5 (0.1)
Rodenticide	4 (0.0)
Herbicide	3 (0.0)
Chelators	1 (0.0)
WMD[b]/riot agent/radiological	1 (0.0)
Cholinergic	0 (0.0)
Fungicide	0 (0.0)
Marine toxin	0 (0.0)
Photosensitizing agents	0 (0.0)
Total agents	9310 (100)

[a] Percentages based on total number of reported agent entries from *N* = 6456 cases; 4662 registry cases (72.2%) reported single agents

[b] *WMD:* Weapon of Mass Destruction

Table 14 Opioids.

	N (%)[a]
Fentanyl	798 (53.9)
Heroin	139 (9.4)
Oxycodone	120 (8.1)
Methadone	104 (7.0)
Opioid Unspecified	101 (6.8)
Buprenorphine	72 (4.9)
Hydrocodone	34 (2.3)
Tramadol	31 (2.1)
Morphine	28 (1.9)
Hydromorphone	14 (0.9)
Codeine	11 (0.7)
Naloxone	8 (0.5)
Naltrexone	6 (0.4)
Miscellaneous[b]	17 (1.1)
Class total	1483 (100)

[a] Percentages based on total number of reported opioid class entries

[b] Includes acetyl fentanyl, depropionylfentanyl, desomorphine, isotonitazene, loperamide, meperidine, N,N-disubstituted piperazine (MT-45), norfentanyl, opium, opium tincture, tapentadol, and U47700

Anticonvulsants, Mood Stabilizers, and Lithium

Lithium was considered its own agent class from other anticonvulsant and mood stabilizer agents (Table 25). Lithium was the most common anticonvulsant and mood stabilizer overall with 83 cases. Among other anticonvulsants/mood stabilizers, valproic acid (24.3%) and lamotrigine (22.5%) were the most commonly reported agents, followed by carbamazepine (13.9%) and phenytoin (9.8%).

Table 15 Ethanol and toxic alcohols.

	N (%)
Ethanol[a]	1384 (100)
Toxic alcohol[b]	
Isopropanol	24 (40.0)
Ethylene glycol	11 (18.3)
Methanol	11 (18.3)
Acetone	5 (8.4)
Miscellaneous[c]	9 (15.0)
Class total	60 (100)

[a] Ethanol is considered a separate agent class

[b] Percentages based on total number of reported toxic alcohol (non-ethanol alcohols and glycols) class entries

[c] Includes diethylene glycol, propylene glycol, benzyl alcohol, ethylene glycol monohexyl ether, and toxic alcohol unspecified

Table 16 Analgesics.

	N (%)[a]
Acetaminophen	801 (67.3)
Ibuprofen	156 (13.1)
Gabapentin	74 (6.2)
Aspirin	61 (5.1)
Acetylsalicylic acid	33 (2.8)
Naproxen	31 (2.6)
Salicylic acid	13 (1.1)
Pregabalin	9 (0.8)
Analgesic unspecified	5 (0.4)
Miscellaneous[b]	7 (0.6)
Class total	1190 (100)

[a] Percentages based on total number of reported analgesic class entries

[b] Includes celecoxib, flurbiprofen, non-steroidal anti-inflammatory (NSAID) unspecified, meloxicam, phenazopyridine, and phenylbutazone

Other Agents

Other agent classes are displayed in order of reported frequency in Supplemental Tables S1-S23.

Clinical Signs and Symptoms

Specific signs and symptoms relating to toxicological exposures are collected within the Core Registry to highlight the manifestations of toxicity from single or multiple agent exposures. These clinical signs and symptoms represent a heterogeneous group of abnormal findings. Each specific sign or symptom has predefined criteria required to be met. Additionally, each case may report more than one clinical sign and symptom within a group or across groups. In 2022, 79.8% ($N = 5750$) of all cases reported at least one sign/symptom. Among the cases with reported signs/symptoms, 84.8% had signs/symptoms that were considered by the medical toxicology physician to be most likely related to a toxic exposure.

Toxidromes

Toxidromes are listed in Table 26. In 2022, 24.6% of the total cases in the Core Registry ($N = 7206$) had at least one toxidrome reported. Among all cases in 2022, opioid toxidromes were the most prevalent (9.2%). Sedative-hypnotic (4.9%), anticholinergic (4.1%), and sympathomimetic (3.1%) were also commonly reported toxidromes.

Table 17 Antidepressants.

	N (%)[a]
Selective serotonin reuptake inhibitors (SSRIs)	368 (43.9)
Sertraline	134 (16.0)
Fluoxetine	102 (12.2)
Escitalopram	76 (9.1)
Citalopram	34 (4.0)
Paroxetine	12 (1.4)
Vilazodone	6 (0.7)
Miscellaneous[b]	4 (0.5)
Other antidepressants	326 (38.9)
Bupropion	205 (24.5)
Trazodone	89 (10.6)
Mirtazapine	27 (3.2)
Miscellaneous[c]	5 (0.6)
Serotonin-norepinephrine reuptake inhibitors (SNRIs)	77 (9.2)
Venlafaxine	42 (5.0)
Duloxetine	25 (3.0)
Desvenlafaxine	9 (1.1)
Miscellaneous[d]	1 (0.1)
Tricyclic Antidepressants (TCAs)	67 (8.0)
Amitriptyline	44 (5.2)
Doxepin	13 (1.6)
Miscellaneous[e]	10 (1.2)
Class total	838 (100)

[a] Percentages based on total number of reported antidepressant class entries

[b] Includes fluvoxamine

[c] Includes antidepressant unspecified, tranylcypromine, and vortioxetine

[d] Includes levomilnacipran

[e] Includes clomipramine, amoxapine, imipramine, desipramine, nortriptyline, and tianeptine

Major Vital Sign Abnormalities

Major vital sign abnormalities with the clinical parameters for each category are listed in Table 27. In 2022, 21.0% of all cases had one or more major vital sign abnormality. Tachycardia (11.3%) was the most common vital sign abnormality among all cases in the Core Registry in 2022, followed by hypotension (5.0%), hypertension (3.6%), bradycardia (3.4%), bradypnea (2.2%), and hyperthermia (0.5%).

Clinical Signs and Symptoms – Neurologic

Neurological signs and symptoms were reported in 44.8% of all 2022 Core Registry cases (Table 28). Coma/CNS depression (19.2%), agitation (13.1%), hyperreflexia/myoclonus/clonus/tremor (10.2%), and delirium/toxic psychosis (7.8%) were the most commonly documented neurological signs and symptoms.

Table 18 Sympathomimetic agents.

	N (%)[a]
Methamphetamine	316 (42.0)
Cocaine	225 (30.0)
Amphetamine	66 (8.8)
Methylphenidate	41 (5.4)
Dextroamphetamine	26 (3.5)
3,4-Methylenedioxymethamphetamine (MDMA), Ecstasy)	21 (2.8)
Lisdexamfetamine	13 (1.7)
Atomoxetine	7 (0.9)
Dexmethylphenidate	6 (0.8)
Phentermine	5 (0.7)
Phenylephrine	5 (0.7)
Miscellaneous[b]	20 (2.7)
Class total	751 (100)

[a] Percentages based on total number of reported sympathomimetic class entries

[b] Includes 2C-T-7 (designer phenethylamine), 3-Fluoroethamphetamine (3-FEA), 4-Fluoroamphetamine (4-FA), alpha-Pyrrolidinopentiophenone (alpha-PVP), cathinone, clenbuterol, diethylpropion, epinephrine, isometheptene, methylenedioxyethylamphetamine (MDE), mixed amphetamine salts, naphazoline, pseudoephedrine, sympathomimetic unspecified, and tetrahydrozoline

Clinical Signs and Symptoms – Pulmonary and Cardiovascular

Pulmonary effects (10.6%) and cardiovascular effects (8.2%) are reported in Table 29. In 2022, among all Core Registry cases respiratory depression (9.3%) and QTc prolongation (6.5%) were the most common pulmonary and cardiovascular effects reported, respectively.

Clinical Signs – Other Organ Systems

Table 30 presents clinical signs involving other organ systems, including renal/musculoskeletal, metabolic, hematologic, gastrointestinal/hepatic, and dermatologic. Among these systems, the two with the most frequently reported manifestations were renal/musculoskeletal (6.7%) and metabolic (6.7%). Among all cases in the Core Registry in 2022 ($N = 7206$), the most commonly observed renal/musculoskeletal effects were acute kidney injury (4.2%) and rhabdomyolysis (3.5%), and the most commonly observed metabolic effects were metabolic acidosis (3.7%) and elevated anion gap (3.2%). Hematologic effects were reported in 6.4% of cases, gastrointestinal/hepatic effects were documented in 5.5%, and dermatologic effects were documented in 2.2%.

Table 19 Sedative-hypnotic/muscle relaxants by type.

	N (%)[a]
Benzodiazepine	350 (63.2)
Alprazolam	127 (22.9)
Clonazepam	81 (14.6)
Lorazepam	44 (8.0)
Diazepam	16 (2.9)
Miscellaneous[b]	22 (4.0)
Benzodiazepine unspecified	60 (10.8)
Muscle Relaxant	114 (20.6)
Baclofen	47 (8.5)
Cyclobenzaprine	35 (6.3)
Tizanidine	13 (2.4)
Methocarbamol	11 (2.0)
Carisoprodol	8 (1.4)
Other Sedatives	50 (9.0)
Buspirone	40 (7.2)
Miscellaneous[c]	7 (1.3)
Sed-Hypnotic/Muscle Relaxant unspecified	3 (0.5)
Non-benzodiazepine agonists ('Z' drugs)	30 (5.4)
Zolpidem	23 (4.1)
Miscellaneous[d]	7 (1.3)
Barbiturates[e]	10 (1.8)
Class total	554 (100)

[a] Percentages based on total number of reported sedative-hypnotic/muscle relaxant class entries

[b] Includes bromazepam, brotizolam, chlorazepate, chlordiazepoxide, clonazolam, clorazepate, etizolam, flubromazepam, midazolam, nitrazepam, and temazepam

[c] Includes phenibut and propofol

[d] Includes eszopiclone and zopiclone

[e] No agent in class with 5 or more occurrences. Includes barbiturate unspecified, butabarbital, butalbital, pentobarbital, and phenobarbital

The most common drugs associated with adverse drug reactions are displayed in Supplemental Table S24.

Fatalities

There were 118 fatalities in 2022, comprising 1.6% of the Core Registry cases. Single agent exposures were implicated in 55 cases (Table 31). Thirty-five cases involved multiple agents (Table 32), and in twenty-eight cases the toxicologic exposure agent(s) were unknown (Table 33). There were 47 fatality cases in which life support was withdrawn, representing 0.7% of Core Registry cases. Brain death was declared in 27 of these cases.

Among the 90 fatalities with known agents, there were 17 (18.9%) involving opioids, with 10 (11.1%) single agent fatalities and 7 (7.8%) multiple agent fatalities.

Table 20 Anticholinergics and antihistamines.

	N (%)[a]
Diphenhydramine	274 (56.3)
Hydroxyzine	103 (21.2)
Benztropine	20 (4.1)
Doxylamine	15 (3.1)
Cetirizine	13 (2.7)
Promethazine	8 (1.6)
Loratadine	7 (1.4)
Dimenhydrinate	6 (1.2)
Pyrilamine	5 (1.0)
Antihistamine unspecified	8 (1.6)
Miscellaneous[b]	28 (5.8)
Class total	487 (100)

[a] Percentages based on total number of reported anticholinergic/antihistamine class entries

[b] Includes anticholinergic unspecified, chlorpheniramine, cinnarizine, cyproheptadine, fesoterodine, homatropine, hyoscyamine, levocetirizine, meclizine, oxybutynin, propantheline, and scopolamine

Acetaminophen was reported in 9 fatalities (10.0%)—of these, 5 (5.6%) cases were single-agent fatalities and 4 (4.4%) were multiple agent fatalities.

In 2022, there were 16 (13.6%) pediatric (age 0–17 years) deaths reported in the Core Registry. Eleven were single-agent exposures, 3 involved multiple agents, and 2 where the exposure agents were unknown. The most commonly implicated agent reported in these pediatric patients was diphenhydramine, associated with 18.8% of pediatric fatalities, with two of the cases reporting diphenhydramine as a single-agent exposure and one case reporting diphenhydramine and dextromethorphan as a multiple agent exposure.

Of note, two patients—one pediatric and one adult— died after exposure to a snakebite. One case reported a single agent exposure to a Crotalus (rattlesnake) and the second was a multiple agent exposure to an unknown type of snake and concomitant cocaine use.

Treatment

Antidotal Therapy

Table 34 describes the 4267 antidotes reported to the Core Registry in 2022. Thiamine (28.3%), folate (24.8%), and N-acetylcysteine (17.2%) were the most commonly reported antidotal therapies.

Antivenom Therapy

Crotalidae polyvalent immune fab (ovine) was again the most commonly reported antivenom (62.9%) in 2022 (Table 35). Crotalidae immune fab_2 (equine) made up 31.9% of the reported antivenom therapy.

Table 21 Cardiovascular agents by type.

	N (%)[a]
Alpha-2 Agonist	136 (29.5)
Clonidine	98 (21.3)
Guanfacine	36 (7.8)
Miscellaneous[b]	2 (0.4)
Beta Blockers	121 (26.3)
Propranolol	47 (10.2)
Metoprolol	34 (7.4)
Carvedilol	25 (5.4)
Atenolol	5 (1.1)
Miscellaneous[c]	10 (2.2)
Calcium Channel Blocker	74 (16.1)
Amlodipine	50 (10.9)
Diltiazem	10 (2.2)
Verapamil	8 (1.7)
Miscellaneous[d]	6 (1.3)
ACEI/ARB	39 (8.5)
Lisinopril	25 (5.4)
Losartan	11 (2.4)
Miscellaneous[e]	3 (0.7)
Other antihypertensives and vasodilators	35 (7.6)
Prazosin	20 (4.4)
Hydralazine	7 (1.5)
Miscellaneous[f]	8 (1.7)
Cardiac Glycosides	23 (5.0)
Digoxin	23 (5.0)
Diuretics	17 (3.7)
Hydrochlorothiazide	9 (2.0)
Miscellaneous[g]	8 (1.7)
Antidysrhythmics and other CV Agents	10 (2.2)
Miscellaneous[h]	10 (2.2)
Antihyperlipidemic	5 (1.1)
Miscellaneous[i]	5 (1.1)
Class total	460 (100)

[a] Percentages based on total number of reported cardiovascular class entries

[b] Includes xylazine

[c] Includes beta blockers unspecified, bisoprolol, labetalol, and nadolol

[d] Includes calcium channel blocker unspecified and nifedipine

[e] Includes isosorbide, minoxidil, nitroprusside, and tamsulosin

[f] Includes benazepril, captopril, and ramipril

[g] Includes amiloride, chlorthalidone, furosemide, and chlorthalidone

[h] No agent in class with 5 or more occurrences. Includes alkyl nitrite, amiodarone, dihydroergotamine, dofetilide, and flecainide

[i] No agent in class with 5 or more occurrences. Includes atorvastatin and rosuvastatin

Table 22 Psychoactives.

	N (%)[a]
Cannabis	114 (32.2)
Tetrahydrocannabinol[b]	110 (31.1)
Gamma hydroxybutyrate	26 (7.3)
Cannabinoid NonSynthetic	17 (4.8)
Cannabinoid Synthetic	14 (4.0)
Nicotine	13 (3.7)
Delta-8-tetrahydrocannabinol	11 (3.1)
Phencyclidine	10 (2.8)
Cannabidiol	9 (2.5)
Ketamine	6 (1.7)
LSD[c]	5 (1.4)
Miscellaneous[d]	19 (5.4)
Class total	354 (100)

[a] Percentages based on total number of reported psychoactive class entries

[b] Tetrahydrocannabinol (cannabis) also includes reports of delta-9-tetrahydrocannabinol

[c] *LSD*: lysergic acid diethylamide

[d] Includes 1,4-Butanediol, 3-Methoxyphencyclidine, 5-MeO-DMT (O-methyl-bufotenin), donepezil, gamma butyrolactone, hallucinogen unspecified, hallucinogenic amphetamines, LAMPA (lysergic acid N,N-methylpropylamide), racetam unspecified, and THC-O acetate (ATHC)

Table 23 Antipsychotics.

	N (%)[a]
Quetiapine	130 (40.5)
Aripiprazole	46 (14.3)
Olanzapine	44 (13.7)
Risperidone	35 (10.9)
Haloperidol	21 (6.5)
Paliperidone	10 (3.2)
Clozapine	8 (2.5)
Lurasidone	6 (1.9)
Miscellaneous[b]	21 (6.5)
Class total	321 (100)

[a] Percentages based on total number of reported antipsychotic class entries

[b] Includes antipsychotic unspecified, asenapine, brexpiprazole, cariprazine, chlorpromazine, droperidol, fluphenazine, loxapine, prochlorperazine, thioidazine, and ziprasidone

Table 24 Envenomations.

	N (%)[a]
Agkistrodon (Copperhead, Cottonmouth/Water moccasin)	114 (39.2)
Crotalus (Rattlesnake)	97 (33.3)
Snake unspecified	33 (11.3)
Loxosceles (Recluse spiders)	20 (6.9)
Miscellaneous snakes[b]	11 (3.8)
Miscellaneous insects and arachnids[c]	9 (3.1)
Miscellaneous scorpions[d]	4 (1.4)
Other miscellaneous envenomations[e]	3 (1.0)
Class total	291 (100)

[a] Percentages based on total number of reported envenomation class entries

[b] Includes Aspidelaps lubricus (Coral Cobra), Dendroaspis (Mamba species), Hydrodynastes gigas (False Water Cobra), Sistrurus (Minor Rattlesnakes incl Pygmy, Massasauga), Thamnophis elegans (Western terrestrial garter snake), Trimeresurus albolabris (var Pit viper incl white lipped, green tree), Trimeresurus unspecified (Pit viper unspecified), and Vipera palaestinae

[c] Includes Hymenoptera (bees, wasps, ants), Latrodectus (widow spiders), and spider unspecified

[d] Includes Centruroides (var Scorpion incl Bark) and Centruroides sculpturatus (Arizona bark scorpion)

[e] Includes animal bite unspecified, envenomation unspecified, and Varanus komodoensis (Komodo dragon)

Table 25 Anticonvulsants and mood stabilizers.

	N (%)
Lithium[a]	83 (100.0)
Other anticonvulsants/mood stabilizers[b]	
Valproic acid	42 (24.3)
Lamotrigine	39 (22.5)
Carbamazepine	24 (13.9)
Phenytoin	17 (9.8)
Topiramate	15 (8.7)
Oxcarbazepine	10 (5.8)
Divalproex	9 (5.2)
Clobazam	5 (2.9)
Miscellaneous[c]	12 (6.9)
Class total	173 (100)

[a] Lithium is considered a separate agent class

[b] Percentages based on total number of reported anticonvulsant and mood stabilizer class entries

[c] Includes anticonvulsant unspecified, brivaracetam, eslicarbazepine, lacosamide, levetiracetam, perampanel, primidone, and zonisamide

Table 26 Toxidromes.

	N (%)[a]
Cases with signs/symptoms, but no toxidrome reported	3965 (55.0)
Cases with one or more toxidromes reported	1775 (24.6)
Total Reported Toxidromes[b]	1912
Opioid	662 (9.2)
Sedative-hypnotic	352 (4.9)
Anticholinergic	296 (4.1)
Sympathomimetic	225 (3.1)
Alcoholic ketoacidosis	186 (2.6)
Serotonin syndrome	120 (1.7)
Sympatholytic	29 (0.4)
Washout syndrome	13 (0.2)
Cholinergic	11 (0.2)
Neuroleptic malignant syndrome	6 (0.1)
Cannabinoid hyperemesis	6 (0.1)
Overlap syndromes	5 (0.1)
Anticonvulsant hypersensitivity	1 (0.0)

[a] Percentage based on number of cases reporting toxidromes relative to total number of registry cases ($N=7206$)

[b] Cases may be associated with more than one toxidrome

Pharmacologic Supportive Care

Table 36 describes the 5012 pharmacologic supportive care treatments reported in 2022. Benzodiazepines (40.6%) were the most common agents used, followed by phenobarbital (14.7%) and opioids (13.5%).

Non-pharmacologic Supportive Care

Intravenous fluid resuscitation (82.7%) and intubation/ventilatory management (14.5%) were the most common treatments in the category of non-pharmacologic supportive care in 2022 (Table 37).

Chelation Therapy

Chelation therapies remained uncommon with 0.2% of Core Registry cases reporting at least one form of chelation therapy administered (Table 38). Dimercaptosuccinic acid (DMSA) was the most commonly reported (66.7%), followed by deferoxamine (26.7%).

Supportive Care—Decontamination Interventions

Table 39 describes the 219 decontamination interventions administered. Activated charcoal represented the majority of interventions representing 91.3% of decontamination interventions, followed by whole-bowel irrigation (6.0%).

Enhanced Elimination Interventions

Among the total number of patients who received enhanced elimination, continuous renal replacement therapy (28.2%) and hemodialysis for toxin removal (27.6%) were the most commonly reported enhanced elimination interventions (Table 40).

Table 27 Major vital sign abnormalities.

	N (%)[a]
Cases with signs/symptoms, but no major vital sign abnormality	4231 (58.7)
Cases with one or more major vital sign abnormality	1509 (21.0)
Total Reported Major Vital Sign Abnormalities[b]	1869
Tachycardia (HR[c] > 140 beats per minute)	816 (11.3)
Hypotension (systolic BP[d] < 80 mmHg)	361 (5.0)
Hypertension (systolic BP[d] > 200 mmHg and/or diastolic BP[d] > 120 mmHg)	258 (3.6)
Bradycardia (HR[c] < 50 beats per minute)	246 (3.4)
Bradypnea (RR[e] < 10 breaths per minute)	155 (2.2)
Hyperthermia (temp > 105° F)	33 (0.5)

[a] Percentage based on number of cases reporting major vital sign abnormalities relative to the total number of registry cases ($N=7206$)

[b] Cases may be associated with more than one major vital sign abnormality

[c] *HR:* heart rate

[d] *BP:* blood pressure

[e] *RR:* respiratory rate

Table 28 Clinical signs and symptoms – neurologic.

	N (%)[a]
Cases with signs/symptoms, but no neurologic effects	2516 (34.9)
Cases with one or more neurologic effects	3224 (44.8)
Total Reported Neurologic Clinical Effects [b]	4498
Coma/CNS depression	1380 (19.2)
Agitation	946 (13.1)
Hyperreflexia/Myoclonus/Clonus/Tremor	733 (10.2)
Delirium/Toxic Psychosis	559 (7.8)
Seizures	399 (5.5)
Hallucination	288 (4.0)
Weakness/Paralysis	84 (1.2)
EPS/Dystonia/Rigidity	59 (0.8)
Numbness/Paresthesia	40 (0.6)
Peripheral Neuropathy (objective)	10 (0.1)

[a] Percentage based on number of cases reporting neurologic effects relative to total number of registry cases ($N=7206$)

[b] Cases may be associated with more than one neurologic effect

Addiction Medicine Treatments

In 2022, addiction medicine treatments were administered by medical toxicologists to 1742 (24.2%) of all cases in the Core Registry (Table 41). The most common addiction medicine treatment was the naloxone overdose (OD) prevention kit or prescription (23.3%) followed by buprenorphine/naloxone dual formulation (e.g. Suboxone) (21.7%).

Table 29 Clinical signs – pulmonary and cardiovascular.

	N (%)[a]
Pulmonary	
Cases with signs/symptoms, but no pulmonary effects	4980 (69.1)
Cases with one or more pulmonary effects	760 (10.6)
Total Reported Pulmonary Effects[b]	840
Respiratory depression	670 (9.3)
Aspiration pneumonitis	92 (1.3)
Acute lung injury/ARDS[c]	48 (0.7)
Asthma/Reactive airway disease	30 (0.4)
Cardiovascular	
Cases with signs/symptoms, but no cardiovascular effects	5153 (71.6)
Cases with one or more cardiovascular effects	587 (8.2)
Total Reported Cardiovascular Effects[b]	698
Prolonged QTc (≥ 500 ms)	468 (6.5)
Prolonged QRS (≥ 120 ms)	117 (1.6)
Myocardial injury or infarction	60 (0.8)
Ventricular dysrhythmia	38 (0.5)
AV Block (> 1st degree)	15 (0.2)

[a] Percentage based on number of cases reporting pulmonary or cardiovascular effects relative to total number of registry cases ($N=7206$)

[b] Cases may be associated with more than one pulmonary or cardiovascular effect

[c] *ARDS*: Acute respiratory distress syndrome

Comparison of the 2022 Annual Report to Previous Annual Reports

For the first time in the ToxIC Core Registry, opioids were designated as the leading agent exposure (15.9%) in 2022. For the second consecutive year, fentanyl (53.9%) was the predominant opioid subclass reported to the Core Registry.

In 2022, there were 118 fatalities reported to the Core Registry. This is comparable to the 120 fatalities reported to the Core Registry in 2021. This is the second consecutive year in which the most common agent class reported in both single-agent and multiple agent fatalities was opioids. The prevalence of opioid exposures among fatalities with known agents in the Core Registry decreased from 2021 to 2022 (24.0% vs. 18.9%, respectively). Fentanyl remained the most commonly implicated agent in single-agent fatalities, reported in 2 pediatric and 6 adult cases. These trends continue to reflect the ongoing opioid epidemic in the United States [19].

The relative frequency of pediatric deaths remained stable from 2021–2022. In 2022, there were 16 (13.6%) pediatric (age 0–17 years) deaths compared to 14 (11.7%) in 2021. In contrast to 2021, the most commonly implicated agent in pediatric fatalities was diphenhydramine (18.8%) with two of the cases reporting diphenhydramine as a single-agent exposure and one case reporting diphenhydramine and dextromethorphan as a multiple agent fatality.

For the first time since the Core Registry started in 2010, there were fatalities reported after snakebite envenomation. Two patients—one pediatric and one adult died after exposure to a snakebite. The pediatric case reported Crotalus (rattlesnake) as a single exposure, and the patient's clinical manifestations included coagulopathy, gastrointestinal bleeding, hypotension, tachycardia, metabolic acidosis, and end organ injury with ultimate cardiac arrest. The adult was a multiple agent exposure to an unknown type of snake and cocaine. Though this patient developed coagulopathy that could be attributed to an envenomation, other clinical findings included sympathomimetic syndrome with hyperthermia. In addition, this patient developed myocardial injury/ischemia.

Discussion

This annual report describes the thirteenth year of data collection for cases seen by medical toxicologists in the ToxIC Core Registry. The Core Registry represents a wide

Table 30 Clinical signs – other organ systems.

	N (%)[a]
Renal/Musculoskeletal	
Cases with signs/symptoms, but no renal/musculoskeletal effects	5256 (72.9)
Cases with one or more renal/musculoskeletal effects	484 (6.7)
Total Reported Renal/Musculoskeletal Clinical Effects[b]	553
Acute kidney injury (creatinine > 2.0 mg/dL)	301 (4.2)
Rhabdomyolysis (CPK[c] > 1000 IU/L)	252 (3.5)
Metabolic	
Cases with signs/symptoms, but no metabolic effects	5261 (73.0)
Cases with one or more metabolic effects	479 (6.7)
Total Reported Metabolic Clinical Effects[b]	645
Metabolic acidosis (pH < 7.2)	265 (3.7)
Elevated anion gap (> 20)	227 (3.2)
Hypoglycemia (glucose < 50 mg/dL)	123 (1.7)
Elevated osmole gap (> 20)	30 (0.4)
Hematologic	
Cases with signs/symptoms, but no hematologic effects	5280 (73.3)
Cases with one or more hematologic effects	460 (6.4)
Total Reported Hematologic Clinical Effects[b]	578
Thrombocytopenia (platelets < 100 K/μL)	177 (2.5)
Hemolysis (Hgb[d] < 10 g/dL)	159 (2.2)
Coagulopathy (PT[e] > 15 s)	115 (1.6)
Leukocytosis (WBC[f] > 20 K/μL)	83 (1.2)
Methemoglobinemia (MetHgb ≥ 2%)	26 (0.4)
Pancytopenia	18 (0.2)
Gastrointestinal/Hepatic	
Cases with signs/symptoms, but no gastrointestinal/hepatic effects	5342 (74.1)
Cases with one or more gastrointestinal/hepatic effects	398 (5.5)
Total Reported Gastrointestinal/Hepatic Clinical Effects[b]	522
Hepatotoxicity (AST[g] ≥ 1000 IU/L)	183 (2.5)
Hepatotoxicity (ALT[h] 100—1000 IU/L)	183 (2.5)
Hepatotoxicity (ALT[h] ≥ 1000 IU/L)	84 (1.2)
Gastrointestinal bleeding	32 (0.4)
Pancreatitis	30 (0.4)
Corrosive injury	8 (0.1)
Intestinal ischemia	2 (0.0)
Dermatologic	
Cases with signs/symptoms, but no dermatologic effects	5584 (77.5)
Cases with one or more dermatologic effects	156 (2.2)
Total Reported Dermatologic Clinical Effects[b]	189
Rash	91 (1.3)
Blister/Bullae	29 (0.7)
Necrosis	33 (0.5)
Angioedema	16 (0.2)

[a] Percentage based on number of cases reporting other organ system effects relative to total number of registry cases ($N = 7206$)

[b] Cases may be associated with more than category effect

[c] *CPK*: creatine phosphokinase

[d] *Hgb:* hemoglobin

[e] *PT:* prothrombin time

[f] *WBC:* white blood cells

[g] *AST:* aspartate aminotransferase

[h] *ALT*: alanine transaminase

Table 31 2022 Fatalities reported in ToxIC Core Registry with known toxicological exposure[a]: Single Agent.

Age / Gender[b]	Agents Involved	Clinical Findings[c]	Life Support Withdrawn	Brain Death Confirmed	Treatment[d]
36 M	Acetaminophen	AG, AKI, CNS, CPT, HPT, HT, MA, PLT, QTC, RBM, TC, WBC	Yes	No	Continuous renal replacement therapy, glucose > 5%, hemodialysis, intubation, IV fluid resuscitation, methylene blue, NAC, vasopressors (epinephrine, norepinephrine, vasopressin), vitamin K
52 F	Acetaminophen	AKI, ALI, CA, CNS, CPT, GIB, HGY, HPT, HT, PLT, PNC, TC	No		Benzodiazepines, continuous renal replacement therapy, CPR, factor replacement, glucose > 5%, intubation, IV fluid resuscitation, NAC, $NaHCO_3$, octreotide, opioids, propofol, steroids, thiamine, transfusion, vasopressors (epinephrine, norepinephrine, phenylephrine, vasopressin)
53 F	Acetaminophen	AG, AKI, CNS, CPT, HGY, HPT, HT, MA, WAS	No		Glucose > 5%, NAC, transfusion
61 M	Acetaminophen	AG, AKI, CPT, HPT, HT, HYS, JD, MA, QTC	Yes	No	Fomepizole, glucose > 5%, glucagon, HIE, intubation, IV fluid resuscitation, NAC, NMB, propofol, transfusion, vasopressors (norepinephrine, vasopressin), vitamin K
79 M	Acetaminophen	None	No		IV fluid resuscitation, NAC, vasopressors (norepinephrine)
17 M	Alprazolam	CNS, HT, SHS	No		None
16 F	Aspirin	None	No		$NaHCO_3$
52 F	Baclofen	AGT, BC, RD, SHS	No		Benzodiazepines, bronchodilators, intubation, IV fluid resuscitation, opioids, propofol
53 F	Bupivacaine	AG, AKI, AP, BC, BP, CA, CNS, HT, MA, QRS, RD, SZ, VD, WBC	Yes	No	Antiarrhythmics, anticonvulsants, antihypertensives, benzodiazepines, calcium, CPR, intubation, IV fluid resuscitation, lipid therapy, $NaHCO_3$, opioids, propofol, therapeutic, vasopressors (epinephrine, norepinephrine)
14 F	Bupropion	CA, CNS, HT, MA, QRS, RD, RFX	Unknown		Anticonvulsants, CPR, intubation, IV fluid resuscitation, $NaHCO_3$, NMB, vasopressors (norepinephrine)
54 F	Carbon monoxide	None	No		None
69 F	Carbon monoxide	ALI, AP, HT, RBM, RD, TC	Unknown		Glucose > 5%, HBO, intubation, IV fluid resuscitation, opioids, vasopressors (epinephrine, norepinephrine)
69 M	Carbon monoxide	AKI, RBM, RD, RFX, TC	Unknown		Intubation, IV fluid resuscitation, propofol
85 M	Carbon monoxide	AVB, CNS, HYT, RFX, TC	No		HBO
69 F	Carvedilol	HT, QTC	No		Atropine, glucagon, IV fluid resuscitation, vasopressors (norepinephrine)
60 F	Citalopram	RFX, SS	Unknown		Benzodiazepines
68 M	Clonazepam	AGT, AVB, HAL, HGY, HPT, PAR	No		Benzodiazepines, glucose > 5%, intubation, IV fluid resuscitation, opioids
57 M	Cocaine	AGT	Unknown		None
74 F	Codeine	BP, CA, CNS, HT, MA, OT, RD	Yes	Yes	Cardioversion, continuous renal replacement therapy, CPR, intubation, NAC, naloxone/nalmefene, propofol, vasopressors (norepinephrine, vasopressin)
74 M	Colchicine	None	Yes	No	None
6 M	Crotalus (Rattlesnake)	AKI, CA, CNS, CPT, GIB, HT, MA, MI, PLT, RBM, RD, TC	Yes	Yes	Benzodiazepines, continuous renal replacement therapy, Fab antivenom, Fab2 antivenom, intubation, transfusion, vasopressors (epinephrine, norepinephrine, vasopressin)
14 F	Diphenhydramine	AC, BC, BP, CNS, MA, RD, SZ, WBC	Yes	Yes	Anticonvulsants, benzodiazepines, intubation, IV fluid resuscitation, NAC, NMB, vasopressors (norepinephrine)
15 F	Diphenhydramine	AC, DLM, QTC, TC	No		None
64 M	Diphenhydramine	CNS	No		Intubation, IV fluid resuscitation

Table 31 (continued)

Age / Gender[b]	Agents Involved	Clinical Findings[c]	Life Support Withdrawn	Brain Death Confirmed	Treatment[d]
26 F	Ethanol	AG, DLM, HPT, HTN, QTC, TC	No		Benzodiazepines, folate, intubation, IV fluid resuscitation, phenobarbital, thiamine
43 M	Ethanol	CNS, HPT, OG, QTC	No		Benzodiazepines, folate, glucagon, IV fluid resuscitation, thiamine
46 M	Ethanol	AKI, CNS, HGY, HT, QTC, RBM	Yes	Unknown	None
61 M	Ethanol	AK, CA, PLT, QTC, TC	No		Acamprosate, benzodiazepines, bronchodilators, CPR, folate, glucagon, IV fluid resuscitation, thiamine
63 M	Ethanol	AKI, HPT, PLT, QRS, QTC, RFX, TC	No		Benzodiazepines, folate, nicotine replacement therapy, phenobarbital, thiamine
63 M	Ethanol	AKI, PLT, QRS, QTC, RFX	No		Benzodiazepines, folate, nicotine replacement therapy, phenobarbital, thiamine
86 M	Ethanol	None	No		Benzodiazepines, folate, IV fluid resuscitation, naltrexone, phenobarbital, thiamine
59 M	Ethylene glycol	MA, RD	Unknown		Continuous renal replacement therapy, fomepizole, hemodialysis for toxin removal, intubation, IV fluid resuscitation, thiamine, vasopressors (epinephrine)
15 M	Fentanyl	BC, CNS, OT, RD, SYS	Yes	Unknown	None
17 M	Fentanyl	AG, AKI, BP, CA, CNS, MA, OT, RBM	Yes	Yes	Anticonvulsants, CPR, intubation, IV fluid resuscitation, naloxone/nalmefene, steroids
23 M	Fentanyl	AKI, BC, BP, CNS, HGY, HPT, HT, MI, OT, QRS, RBM, RD, TC, VD	No		Continuous renal replacement therapy, glucose > 5%, IV fluid resuscitation, ketamine, naloxone/nalmefene, opioids, therapeutic hypothermia, vasopressors (norepinephrine, phenylephrine vasopressin)
37 F	Fentanyl	None	Yes	Yes	Buprenorphine/naloxone, intubation, opioids, propofol, steroids, vasopressors (epinephrine, norepinephrine, vasopressin)
39 F	Fentanyl	AG, AKI, CA, CNS, CPT, HPT, HT, MA, OT, PCT, QRS, QTC, RD, VD, WBC	Yes	Yes	Antiarrhythmics, balloon pump, benzodiazepines, defibrillation, CPR, intubation, $NaHCO_3$, naloxone/nalmefene, vasopressors (norepinephrine)
41 M	Fentanyl	OT	Unknown		IV fluid resuscitation, methadone, opioids
44 F	Fentanyl	OT, RD, MHG	No		None
49 M	Fentanyl	HPT, MA, OT, RD, RFX	No		Intubation, IV fluid resuscitation, NAC
83 F	Flecainide	TC	Unknown		Magnesium
1 mo F	Homeopathic remedy unspecified	MA	Unknown		IV fluid resuscitation
22 F	Iron	BC	No		IV fluid resuscitation
23 mo M	Iron	BP, CNS, HT, MA, TC	Yes	Yes	Benzodiazepines, deferoxamine, ECMO, hemodialysis, IV fluid resuscitation, NMB, opioids, steroids, vasopressors (dopamine, epinephrine, norepinephrine), whole bowel irrigation
64 F	Metformin	AG, AKI, HT, MA, OG, QTC, WBC	No		Benzodiazepines, continuous renal replacement therapy, intubation, IV fluid resuscitation, $NaHCO_3$, steroids, thiamine, vasopressors (epinephrine, norepinephrine, vasopressin)
64 F	Metformin	AG, AKI, CNS, CPT, DLM, HG, HPT, HT, HYS, MA, OG, PLT, QTC, RBM, WBC	Yes	Yes	Continuous renal replacement therapy, glucose > 5%, intubation, IV fluid resuscitation, methylene blue, $NaHCO_3$, vasopressors (epinephrine, norepinephrine, vasopressin)
72 F	Metformin	AG, AKI, HT, MA, TC	No		Continuous renal replacement therapy, IV fluid resuscitation, $NaHCO_3$, vasopressors (epinephrine, norepinephrine)

Table 31 (continued)

Age / Gender[b]	Agents Involved	Clinical Findings[c]	Life Support Withdrawn	Brain Death Confirmed	Treatment[d]
75 F	Metformin	AG, AKI, CNS, HTN, MA, PAR, RBM, SZ, TC	Yes	Yes	Antiarrhythmics, benzodiazepines, bronchodilators, continuous renal replacement therapy, intubation, IV fluid resuscitation, $NaHCO_3$, opioids, propofol, vasopressors (norepinephrine, phenylephrine, vasopressin)
32 F	Methadone	OT, RD	No		Methadone
43 F	Methamphetamine	OT, RD	No		None
16 M	Methanol	AG, BC, CNS, HT, RD	Yes	Yes	Folate, fomepizole, intubation, IV fluid resuscitation, propofol, thiamine
31 M	Mixed Amphetamine Salts	CNS, HTN	Yes	Yes	Antihypertensives, intubation
70 F	Morphine	BP, CNS, HYS, PLT	Unknown		IV fluid resuscitation, naloxone/nalmefene
66 M	Nadolol	HYS, MA, QTC, RD	Unknown		Intubation, IV fluid resuscitation, opioids
47 F	Tafenoquine	AG, CNS, MA, MHG, PLT, QTC	Unknown		Intubation, NMB

[a] Based on response from Medical Toxicologist "Did the patient have a toxicological exposure?" equals Yes with known agent(s)

[b] Age in years unless otherwise stated. mo: months

[c] AC: anticholinergic, AG: anion gap, AGT: agitation, AK: alcoholic ketoacidosis, AKI: acute kidney injury, ALI: acute lung injury/ARDS, AP: aspiration pneumonitis, AVB: AV block, BC: bradycardia, BP: bradypnea, CA: cardiac arrest, CNS: coma/CNS depression, CPT: coagulopathy, DLM: delirium, GIB: GI bleeding, HAL: hallucination, HGY: hypoglycemia, HPT: hepatotoxicity, HT: hypotension, HTN: hypertension, HYS: hemolysis, HYT: hyperthermia, JD: jaundice, MA: metabolic acidosis, MHG: methemoglobinemia, MI: myocardial injury/ischemia, OG: osmolar gap, OT: opioid toxidrome, PAR: paralysis/weakness, PCT: pancytopenia, PLT: thrombocytopenia, PNC: pancreatitis, QRS: QRS prolongation, QTC: QTc prolongation, RBM: rhabdomyolysis, RD: respiratory depression, RFX: hyperreflexia/clonus/tremor, SHS: sedative-hypnotic syndrome, SS: serotonin syndrome, SYS: sympathomimetic syndrome, SZ: seizures, TC: tachycardia, VD: ventricular dysrhythmia, WBC: leukocytosis

[d] Pharmacological and Non-pharmacological support as reported by Medical Toxicologist; CPR: cardiopulmonary resuscitation, ECMO: extra-corporeal membrane oxygenation, HBO: hyperbaric oxygenation, HIE: high dose insulin euglycemic therapy, NAC: n-acetyl cysteine, $NaHCO_3$: sodium bicarbonate, NMB: neuromuscular blockers

Table 32 2022 Fatalities reported in ToxIC Core Registry with known toxicological exposure[a]: Multiple Agents.

Age / Gender[b]	Agents Involved	Clinical Findings[c]	Life Support Withdrawn	Brain Death Confirmed	Treatment[d]
83 F	Acetaminophen, aspirin	AKI, HT, RD	Yes	No	IV fluid resuscitation, NAC
46 F	Acetaminophen, aspirin, phentermine	CNS, HGY, MA, QTC, RBM, RD, SYS, TC	Yes	Yes	Benzodiazepines, glucose > 5%, intubation, IV fluid resuscitation, NAC, opioids, propofol
24 F	Acetaminophen, bupropion, lisdexamfetamine	CNS, HPT, HT, RAD	Yes	No	Benzodiazepines, dexmedetomidine, fomepizole, intubation, IV fluid resuscitation, NAC, vitamin K
23 M	Acetaminophen, cocaine, oxycodone	AKI, BC, CA, CNS, HPT, HTN, HYT, MA, QTC, RD, WBC	Yes	Yes	Calcium, continuous renal replacement therapy, CPR, intubation, IV fluid resuscitation, NAC, $NaHCO_3$, vasopressors (epinephrine, norepinephrine)
64 M	Acetone, benzodiazepine unspecified, ethanol, ketamine, methanol, valproic acid	AKI, CNS, HGY, HT, QTC, RD, SZ	Yes	Yes	Activated charcoal, hemodialysis, intubation, IV fluid resuscitation
24 F	Albuterol, famotidine, lorazepam, ondansetron, scopolamine	AC, TC	No		Benzodiazepines, IV fluid resuscitation
18 F	Amlodipine, benazepril, ranitidine	CNS, MA	No		Glucagon, HIE, hydroxocobalamin, intubation, IV fluid resuscitation, lipid therapy, $NaHCO_3$, vasopressors (angiotensin, epinephrine, norepinephrine, vasopressin)
75 M	Amlodipine, carvedilol	BC, CPT, PLT, QRS, QTC	No		None
54 M	Amlodipine, metformin, propranolol	AG, AKI, CNS, CPT, HT, MA, RD	No		Continuous renal replacement therapy, intubation, IV fluid resuscitation, methylene blue, vasopressors (epinephrine, norepinephrine)
54 M	Amlodipine, metoprolol	BC, HT	Yes	Yes	Activated charcoal, balloon pump, calcium, continuous renal replacement therapy, CPR, ECMO, glucagon, glucose > 5%, HIE, intubation, IV fluid resuscitation, methylene blue, pacemaker, propofol, transfusion, vasopressors (epinephrine, milrinone, norepinephrine, vasopressin)
25 F	Amphetamine, cocaine	AG, AKI, ALI, BP, CA, CNS, HPT, HT, MA, MI, RBM	Yes	Yes	CPR, intubation, vasopressors (norepinephrine, vasopressin)
25 F	Apixaban, codeine, flecainide	AG, ALI, BC, CNS, HT, MA, QRS, QTC, RBM, RD, VD	No		Antiarrhythmics, atropine, cardioversion, continuous renal replacement therapy, CPR, ECMO, factor replacement, glucose > 5%, HIE, intubation, IV fluid resuscitation, lipid therapy, $NaHCO_3$, vasopressors (epinephrine, norepinephrine, phenylephrine, vasopressin)
31 F	Bupropion, ethanol, fluoxetine, rizatriptan	QTC, RFX	No		Benzodiazepines, propofol
38 F	Bupropion, lamotrigine	CNS, HT	Yes	No	IV fluid resuscitation
53 M	Carbon monoxide, Cyanide	ALI, CNS, HPT, HT, MI, RBM, TC	Yes	No	Hydroxocobalamin, vasopressors (epinephrine, norepinephrine, phenylephrine)

Table 32 (continued)

Age / Gender[b]	Agents Involved	Clinical Findings[c]	Life Support Withdrawn	Brain Death Confirmed	Treatment[d]
Unknown M	Carbon monoxide, Cyanide	AG, ALI, CNS, HT, MA, RBM	No		Benzodiazepines, hydroxocobalamin, IV fluid resuscitation, NMB, propofol
74 M	Carvedilol, hydralazine	AKI, BC, CNS, CPT, HPT, HT, MA, PLT, QRS, QTC, VD	No		Continuous renal replacement therapy, CPR, glucagon, intubation, IV fluid resuscitation, $NaHCO_3$, pacemaker, propofol, vasopressors (epinephrine, norepinephrine, phenylephrine, vasopressin)
80 M	Clonidine, zolpidem	MA, RD, SHS	No		IV fluid resuscitation, naloxone/nalmefene
35 M	Cocaine, cyclobenzaprine, ethanol, lorazepam	RD	No		Intubation, IV fluid resuscitation
43 M	Cocaine, fentanyl	None	Unknown		Buprenorphine/naloxone, clonidine, IV fluid resuscitation
32 F	Cocaine, gamma butyrolactone	AG, ALI, BP, CNS, CPT, HPT, HT, MA, MI, OT, PLT, QRS, QTC, RD, SHS, VD	Yes	Yes	Calcium, CPR, dexmedetomidine, intubation, IV fluid resuscitation, $NaHCO_3$, naloxone/nalmefene, transplantation
35 F	Cocaine, gamma hydroxybutyrate, ketamine, MDMA (methylenedioxy-N-methamphetamine, ecstasy)	AG, ALI, CNS, CPT, GII, HPT, HT, HTN, MA, PLT, QRS, QTC, RD, SHS, VD	Yes	Yes	Antihypertensives, CPR, dexmedetomidine, intubation, IV fluid resuscitation, $NaHCO_3$, naloxone/nalmefene, propofol, vasopressors (epinephrine)
20 F	Cocaine, MDMA (methylenedioxy-N-methamphetamine, ecstasy)	CNS, CPT, HPT, HT, HYT, RBM, SS, TC	Yes	Yes	Benzodiazepines, continuous renal replacement therapy, cyproheptadine, ECMO, opioids, propofol, vasopressors (metaradrine, norepinephrine)
37 M	Cocaine, methamphetamine	AGT, SYS, TC	No		Antipsychotics, benzodiazepines, IV fluid resuscitation, ketamine
47 M	Cocaine, methamphetamine	AKI, CNS, MI, QRS, RBM, VD	Yes	Yes	Benzodiazepines, IV fluid resuscitation, NAC
42 M	Cocaine, snake unspecified	AK, AKI, CNS, CPT, HPT, HT, HTN, HYT, MA, MI, PLT, RBM, SYS, SZ, TC	Yes	No	Benzodiazepines, Fab antivenom, glucose > 5%, hemodialysis, intubation, IV fluid resuscitation, NMB, propofol, vasopressors (epinephrine, norepinephrine, phenylephrine, vasopressin)
14 M	Dextromethorphan, diphenhydramine	RFX	Unknown		None
73 T	Digoxin, ethanol	AKI, BC, HT	Yes	Unknown	Folate, thiamine
30 F	Fentanyl, methamphetamine	OT, RBM, RD, SYS	Yes	Yes	Intubation, IV fluid resuscitation, naloxone/nalmefene, opioids, propofol
31 M	Fentanyl, methamphetamine	AG, AGT, AP, BLB, DLM, HPT, OT, RBM, SYS	Yes	Yes	None
37 F	Fentanyl, oxycodone	CNS, HTN, OT, RBM, RD	Yes	Unknown	Intubation, IV fluid resuscitation
17 F	Gabapentin, lamotrigine	BC, HT	No		Atropine, IV fluid resuscitation

Table 32 (continued)

Age / Gender[b]	Agents Involved	Clinical Findings[c]	Life Support Withdrawn	Brain Death Confirmed	Treatment[d]
10 F	Herbal (dietary) multibotanical, Soursop (Annona muricata, Graviola)	AG, AKI, AP, CNS, HT, MA, MI, OG, TC	Yes	Yes	CPR, intubation, IV fluid resuscitation, vasopressors (epinephrine, norepinephrine, vasopressin)
30 M	Heroin, methadone	AG, BP, CA, CNS, HT, MA, MI, QTC, RD, SYL	Yes	Yes	Anticonvulsants, CPR, intubation, IV fluid resuscitation, naloxone/nalmefene, propofol, vasopressors (norepinephrine)
71 M	Lorazepam, oxycodone	DLM, SHS, WBC	No		Antipsychotics, benzodiazepines, naloxone/nalmefene, nicotine replacement therapy

[a] Based on response from Medical Toxicologist "Did the patient have a toxicological exposure?" equals Yes with known agent(s)

[b] Age in years unless otherwise stated

[c] AC: anticholinergic, AG: anion gap, AGT: agitation, AK: alcoholic ketoacidosis, AKI: acute kidney injury, ALI: acute lung injury/ARDS, AP: aspiration pneumonitis, BC: bradycardia, BL: blisters/bullae, BP: bradypnea, CA: cardiac arrest, CNS: coma/CNS depression, CPT: coagulopathy, DLM: delirium, GI: intestinal ischemia, HGY: hypoglycemia, HPT: hepatoxicity, HT: hypotension, HTN: hypertension, HYT: hyperthermia, MA: metabolic acidosis, MI: myocardial injury/ischemia, OG: osmolar gap, OT: opioid toxidrome, PLT: thrombocytopenia, QRS: QRS prolongation, QTC: QTc prolongation, RAD: asthma/reactive airway disease, RBM: rhabdomyolysis, RD: respiratory depression, RFX: hyperreflexia/clonus/tremor, SHS: sedative-hypnotic syndrome, SS: serotonin syndrome, SYL: sympatholytic syndrome, SYS: sympathomimetic syndrome, SZ: seizures, TC: tachycardia, VD: ventricular dysrhythmia, WBC: leukocytosis

[d] Pharmacological and Non-pharmacological support as reported by Medical Toxicologist; CPR: cardiopulmonary resuscitation, ECMO: extra-corporeal membrane oxygenation, HIE: high dose insulin euglycemic therapy, NAC: n-acetyl cysteine, $NaHCO_3$: sodium bicarbonate, NMB: neuromuscular blockers

geographical distribution of cases evaluated by medical toxicologists, including sites in each U.S. Census Bureau designated region and 4 sites internationally. The Core Registry can be used to evaluate poisoning trends, identify novel exposures, explore relationships with concomitant public health crises, and assess the public health implications of rare exposures on a large scale.

Opioids were the most commonly reported agent exposure for the first time in the ToxIC Core Registry, with fentanyl as the leading agent within the opioid class. Prior to 2021, the most prevalent opioid agent exposure in the Core Registry was heroin [10, 11]. These observations are consistent with national trends [19, 20], and may also be a reflection of improved capacity for hospital-based laboratory testing which allows for increased detection of fentanyl.

ToxIC continues to make advancements to the Core Registry. In 2022, the Core Registry included additional demographic and social characteristic variables of patients seen by medical toxicology physicians. The recently added variables in 2022 (past medical history, past surgical history, and past misuse) all strengthen the Core Registry data to increase our understanding of risk and protective factors associated with poisoning exposures, treatment, and outcomes.

Limitations

The ToxIC Core Registry is a rich database of cases in which patient consultations are performed by medical toxicology physicians, enabling an informed relationship between exposures and clinical outcomes; however, limitations to the Core Registry do exist. One possible limitation is a bias towards inclusion of more severe case presentations, as cases are only included if they undergo subspecialty consultation. Cases for which a medical toxicology consultation was not requested may represent a group with less severe illness. Therefore, the Core Registry likely represents a different population from other data sources, such as those maintained by Poison Centers [21]. However, compared with Poison Center data, the Core Registry consists of data collection by medical toxicology physicians after a first-hand evaluation of the patient, leading to detailed data on exposure, treatment, and patient characteristics. Regional differences may lead to a disproportionate number of specific cases reported based on variations in drug use, misuse, and other toxic exposures. The ToxIC Core Registry includes sites from multiple diverse locations, but the entire country is not uniformly represented. Specifically, the ToxIC Core Registry consists of large, academic medical centers with high numbers of medical toxicology faculty which may be systematically different from smaller, community-based healthcare systems without medical toxicologists. Most ToxIC sites also sponsor a medical toxicology fellowship training program, which may also contribute to differences in medical centers.

Table 33 2022 Fatalities reported in ToxIC Core Registry with unknown toxicological exposure[a].

Age / Gender[b]	Clinical Findings[c]	Life Support Withdrawn	Brain Death Confirmed	Treatment Reported[d]
3 F	CNS, HPT, TC	Yes	No	None
16 F	CNS, HT, RD	Yes	Yes	None
26 M	None	Yes	Unknown	None
29 M	CPT, DLM, EPS, HYT, PLT, RBM, RFX, SS, SYS, VD	No		Benzodiazepines, intubation, IV fluid resuscitation, $NaHCO_3$, vasopressors (epinephrine, norepinephrine, vasopressin)
30 F	AG, AKI, ALI, CNS, HT, MA, PLT, QTC	Yes	No	Intubation, naloxone/nalmefene, vasopressors (epinephrine, norepinephrine)
44 F	None	Unknown		None
44 M	RD	No		None
45 M	ALI, CNS, HT, HYT	Unknown		Benzodiazepines, ECMO, intubation, IV fluid resuscitation, ketamine, NMB, opioids, vasopressors (norepinephrine)
50 F	QTC	Yes	Unknown	Benzodiazepines, folate, IV fluid resuscitation, thiamine
52 F	None	Yes	Yes	Benzodiazepines, buprenorphine/naloxone, IV fluid resuscitation, naloxone/nalmefene
54 M	BC, CNS, HGY, RD	Unknown		Glucagon, intubation, IV fluid resuscitation
56 M	None	Unknown		None
57 M	AG, AKI, CNS, HT, MA, OG, RBM, RD	No		None
58 F	None	Unknown		None
58 M	AG, AKI, CNS, HPT, HT, MA	Yes	No	Fomepizole, intubation, IV fluid resuscitation, vasopressors (norepinephrine, vasopressin)
60 F	None	No		None
60 M	AG, BC, CNS, HT, MA	Yes	Unknown	Intubation, IV fluid resuscitation, vasopressors (norepinephrine, vasopressin)
61 M	None	Yes	Yes	None
65 F	None	Yes	Unknown	None
65 M	AG, CNS, HGY, HPT, HYT, MA, VD	No		None
66 M	None	Unknown		IV fluid resuscitation, thiamine
68 F	AG, AKI, CNS, HGY, HPT, HT, HYS, MA, PLT	Yes	No	Antiarrhythmics, benzodiazepines, continuous renal replacement therapy, glucose > 5%, intubation, IV fluid resuscitation, NAC, $NaHCO_3$, opioids, transfusion, vasopressors (norepinephrine)
69 F	None	Unknown		None
69 M	PLT, QTC	Unknown		Anticonvulsants, buprenorphine, buprenorphine/naloxone, clonidine, dexmedetomidine, folate, glucagon, IV fluid resuscitation, $NaHCO_3$, naloxone/nalmefene
74 F	None	Unknown		None
77 F	AGT, AKI, RD	No		Continuous renal replacement therapy
80 M	NMS	Unknown		Intubation, IV fluid resuscitation
86 M	AG, AGT, RD, RFX	Unknown		None

[a] Based on response from Medical Toxicologist "Did the patient have a toxicological exposure?" equals No or Unknown

[b] Age in years unless otherwise stated

[c] AG: anion gap, AGT: agitation, AKI: acute kidney injury, ALI: acute lung injury/ARDS, BC: bradycardia, CNS: coma/CNS depression, CPT: coagulopathy, DLM: delirium, EPS: extrapyramidal symptoms/dystonia/rigidity, HGY: hypoglycemia, HPT: hepatoxicity, HT: hypotension, HYS: hemolysis, HYT: hyperthermia, MA: metabolic acidosis, NMS: neuroleptic malignant syndrome, OG: osmolar gap, PLT: thrombocytopenia, QTC: QTc prolongation, RBM: rhabdomyolysis, RD: respiratory depression, RFX: hyperreflexia/clonus/tremor, SS: serotonin syndrome, SYS: sympathomimetic syndrome, TC: tachycardia, VD: ventricular dysrhythmia

[d] Pharmacological and Non-pharmacological support as reported by Medical Toxicologist; ECMO: extra-corporeal membrane oxygenation, NAC: n-acetyl cysteine, $NaHCO_3$: sodium bicarbonate, NMB: neuromuscular blockers

Table 34 Antidotal therapy.

	N (%)[a]
Thiamine	1209
Folate	1058
N-acetylcysteine	736
Naloxone/nalmefene	471
Sodium bicarbonate	160
Fomepizole	121
Glucagon	113
Calcium	105
Flumazenil	50
Vitamin K	34
Atropine	32
Octreotide	31
Cyproheptadine	26
Methylene blue	26
Insulin-euglycemic therapy	18
Physostigmine	14
Carnitine	13
Lipid resuscitation therapy	11
Fab for digoxin	7
Factor replacement	7
Pyridoxine	6
Hydroxocobalamin	6
Anticoagulation reversal	2
Botulinum antitoxin	2
Bromocriptine	2
Dantrolene	2
Thiosulfate	2
Uridine triacetate	1
Silymarin/silibinin	1
Protamine	1
Total	**4267**

[a] 2762 registry cases (38.3%) received at least one antidote. Cases may have involved the use of multiple antidotes

Table 35 Antivenom treatment.

	N (%)[a]
Crotalidae polyvalent immune fab (ovine)	134 (62.9)
Crotalidae immune fab_2 (equine)	68 (31.9)
Other snake antivenom	5 (2.4)
Scorpion antivenom	4 (1.9)
Spider antivenom	2 (0.9)
Total	213 (100)

[a] Percentages based on total number of antivenom treatments administered ($N=213$); 204 registry cases (2.8%) received at least one antivenom treatment. Cases may have involved the use of multiple antivenom treatments

Table 36 Supportive care-pharmacologic.

	N (%)[a]
Benzodiazepines	2034 (40.6)
Phenobarbital	736 (14.7)
Opioids	676 (13.5)
Propofol	325 (6.5)
Antipsychotics	224 (4.4)
Vasopressors	212 (4.2)
Dexmedetomidine	145 (2.9)
Glucose > 5%	136 (2.7)
Anticonvulsants	120 (2.4)
Albuterol and other bronchodilators	88 (1.8)
Neuromuscular blockers	79 (1.6)
Ketamine	69 (1.4)
Beta-blockers	53 (1.0)
Antihypertensives	50 (1.0)
Steroids	44 (0.9)
Antiarrhythmics	15 (0.3)
Vasodilators	6 (0.1)
Total	5012 (100)

[a] Percentages based on total number of pharmacologic interventions ($N=5012$); 3097 registry cases (43.0%) received at least one pharmacologic intervention. Cases may have involved the use of multiple interventions

At the level of the individual sites, there may be a reporting bias towards more complicated or interesting cases. Although the Core Registry's principal goal, as defined in written agreements with all sites, is to obtain a consecutive

Table 37 Supportive care–nonpharmacologic.

	N (%)[a]
IV fluid resuscitation	3517 (82.7)
Intubation/ventilatory management	615 (14.5)
CPR[b]	39 (0.9)
Transfusion	31(0.7)
Hyperbaric oxygen	14 (0.3)
ECMO[c]	11 (0.3)
Transplant	9 (0.2)
Pacemaker	6 (0.1)
Therapeutic hypothermia	5 (0.1)
Cardioversion	5 (0.1)
Balloon pump	2 (0.1)
Total	4254 (100)

[a] Percentages based on total number of treatments administered ($N=4254$); 3659 registry cases (50.8%) received at least one form of nonpharmacologic treatment. Cases may have involved the use of multiple forms of treatment

[b] *CPR:* Cardiopulmonary resuscitation

[c] *ECMO:* extracorporeal membrane oxygenation

Table 38 Chelation therapy.

	N (%)[a]
DMSA[b]	10 (66.7)
Deferoxamine	4 (26.7)
BAL[c]	1 (6.6)
Total	15 (100)

[a] Percentages based on total number of chelation treatments administered ($N=15$); 15 registry cases (0.2%) received at least one form of chelation treatment

[b] *DMSA:* dimercaptosuccinic acid

[c] *BAL:* British anti-Lewisite (dimercaprol)

Table 39 Supportive care-decontamination.

	N (%)[a]
Activated charcoal	200 (91.3)
Whole bowel irrigation	13 (6.0)
Irrigation	4 (1.8)
Gastric lavage	2 (0.9)
Total	219 (100)

[a] Percentages based on total number of decontamination interventions ($N=219$); 218 registry cases (3.0%) received at least one decontamination intervention. Cases may have involved the use of multiple interventions

sample of all cases at a given site, individual cases may be missed. Any observations of trend differences between past annual reports and the 2022 annual report may be driven by the proportion of cases attributed to each site. Analyses are ongoing to examine trends across time within the Core Registry and to determine intraclass correlations for similarities of cases within each site. Though the Core Registry is not population-based, it serves as a strong adjunct to evaluate public health or clinical trends.

Table 40 Enhanced elimination.

	N (%)[a]
Continuous renal replacement therapy	44 (28.2)
Hemodialysis (toxin removal)	43 (27.6)
Hemodialysis (other indication)	35 (22.4)
Urinary alkalinization	26 (16.7)
Multiple-dose activation charcoal	7 (4.5)
Exchange transfusion	1 (0.6)
Total	156 (100)

[a] Percentages based on total number of treatments administered ($N=156$); 142 registry cases (2.0%) received at least one form of enhanced elimination. Cases may have involved the use of multiple

Table 41 Addiction medicine treatments.

	N (%)[a]
Naloxone overdose prevention kit or prescription	604 (23.3)
Buprenorphine/naloxone dual formulations (e.g. Suboxone)	561 (21.7)
Nicotine replacement therapy (patch, gum, etc.)	443 (17.1)
Methadone	293 (11.3)
Naltrexone	264 (10.2)
Clonidine	195 (7.5)
Other specify—Outpatient abuse services/recovery care	91 (3.5)
Buprenorphine w/o opioid antagonist (e.g. Subutex)	85 (3.3)
Acamprosate	49 (1.9)
Disulfiram	3 (0.1)
Total	2588 (100)

[a] Percentages based on total number of treatments administered ($N=2588$); 1742 registry cases (24.2%) received at least one form of addiction medicine treatment. Cases may have involved the use of multiple addiction medicine treatments

Data regarding substances of exposure, intent of exposure, and species of envenomations relies heavily on patient self-report and may be misclassified; this limitation is likely most significant for self-reported illicit drug exposure and intention of drug exposure, which are subject to both recall and social desirability bias. However, all data available are utilized to evaluate the agent of exposure after the medical toxicology physician evaluation, including patient self-report, physical exam, and available laboratory testing. Additionally, demographic information may be misclassified by toxicologists when patients are unconscious or unable to self-identify gender, race, or ethnicity. Lastly, efforts are made to continually improve the quality of data collected. While member sites are instructed to complete all applicable data fields and most data fields are mandatory, cases and data fields with incomplete information are still possible. This remains an issue for housing data, for example. Efforts continue to support quality data collection and follow up on missing data where applicable.

Conclusions

The ToxIC program continues to grow and evolve, including adaptations and expansion of the Core Registry, the creation of additional sub-registries, and the evolution of other projects outside of the Core Registry. The Core Registry remains a distinct data source consisting of cases evaluated by medical toxicology physicians, yielding a large database for poisonings with the potential for high-quality data analysis of detailed demographic, clinical, and treatment data.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13181-023-00962-2.

Acknowledgements Toxicology Investigators Consortium (ToxIC) Study Group Collaborators:

Jennifer Acciani, Elizabeth Adeyeye, Peter Akpunonu, Timothy Albertson, Adam Algren, John Archer, Sukhshant Atti, Robert Avera, Kavita Babu, Alexander Baer, Klara De Baerdemaeker, Fatma Al Balushi, Hassan Al Balushi, Kevin Baumgartner, Gillian Beauchamp, Vik Bebarta, Melisa Lai Becker, Noah Berland, David Betting, Michael Beuhler, Steven Bird, Matthew Blundell, Heather Borek, Evan Bradley, Nicklaus Brandehoff, Marielle Brenner, Daniel Brooks, Jennie Buchanan, Michele Burns, Alfred Cahana, Diane Calello, Vincent Calleo, Alexa Camarena-Michel, Joshua Canning, Dazhe Cao, Jennifer Carey, Joshua Carlson, Joseph Carpenter, Stephanie Carreiro, Emma Cassidy, Jorge Castaneda, Rachel Castelli, Trevor Cerbini, Edward Certaruk, Nathan Charlton, Richard Chen, James Chenoweth, Samy Chettat, Michael Christian, Richard Church, Joseph Clemons, Daniel Colby, Ryan Cole, Grant Comstock, Albert Conicella, Matthew Cook, Matthew Correia, Robert Cox, Steven Curry, Arthur Daigh, Paul Dargan, John Delbianco, Jason Devgun, Christopher Dion, William Dribben, Bernard Eisenga, Lindsey Claire Epperson, Rita Farah, Henry Farrar, Chris Feng, Sing-Yi Feng, Derek Fikse, Jonathan Ford, Carolyn Fox, Keith French, Blake Froberg, Jakub Furmaga, Melissa Gittinger, David Goldberger, Will Goodrich, Kimberlie Graeme, Powell Graham, Kevin Greene, Spencer Greene, Howard Greller, Matt Griswold, Stacey Hail, Thao-Phuong Christy Hallett, Laurie Halmo, Riley Hartmann, Benjamin Hatten, Kennon Heard, Will Heise, Robert Hendrickson, Reynaldo Hernandez, Michelle Hieger, Ruby Hoang, Michael Hodgman, Christopher Holstege, Jason Hoppe, Zane Horowitz, Christopher Hoyte, Adrienne Hughes, Laura Hunter, Katie Hurlbut, Zachary Illg, Janetta Iwanicki, Laura James, Mohamed Jefri, LilyAnne Jewett, Brett Johnson, David Johnson, Chase Jones, Seth Jones, Bryan Judge, Sasha Kaiser, Min Kang, Louise Kao, Sabrina Kaplan, Kenneth Katz, Ziad Kazzi, Mike Keenan, Abigail Kerns, Yasmeen Khaskia, Emily Kiernan, Ronald Kirschner, Kurt Kleinschmidt, Natalie Ebeling Koning, Andrew Koons, Michael Kosnett, James Krueger, Jessica Krueger, Shana Kusin, Jeffrey Lai, Rebecca Latch, Eric Lavonas, Jake Lebin, Michael Levine, Brian Lewis, Erica Liebelt, David Liss, Steve Liu, Chin-Yu Lo, Annette Lopez, David Loughran, Scott Lucyk, Shawn Luo, Yael Lurie, Sarah Mahonski, Greg Makar, Kevan J Mamdouhi, Michael Marlin, Stacy Marshall, Kelsey Martin, Nik Matsler, Serah Mbugua, Charles McElyea, Eric McGillis, Christopher Meaden, Andrew Micciche, Avery Michienzi, Christopher Mitchell, Andrew Monte, Brent Morgan, Michael Mullins, Karen Muschler, Nicholas Nacca, Kristine Nanagas, Lewis Nelson, Natalie Neumann, HoanVu Nguyen, Tuyet-Anh Nguyen, Supa Niruntarai, Ayrn O'Connor, Katherine O'Donnell, Jonathan De Olano, Rittirak Othong, Jenna Otter, Daniel Ovakim, Kelly Owen, Mehruba Parris, Lesley Pepin, Dimitry Petrenko, Todd Phillips, Christopher Pitotti, Lawrence Quang, Tony Rianprakaisang, Mark Rigatti, Morgan Riggan, Bradley Riley, Daniel Rivera, Brett Roth, Ann-Michelle Ruha, William Rushton, Steven Salhanick, Cynthia Santos, David Schaffer, Pieter Scheerlinck, Evan Schwarz, Kerollos Shaker, Elizabeth Shanahan, Kapil Sharma, Sophia Sheikh, Mark Simon, Michael Simpson, Serge Simpson, Miya Smith, Jerry Snow, Arjumand Sohaila, Hannah Spungen, Alaina Steck, Jennifer Stephani, Kyle Suen, Suad Al Sulaimahi, Ross Sullivan, Lachlan Sund, Ryan Surmaitis, Courtney Temple, John Thompson, Stephen Thornton, Lisa Thurgur, Nicholas Titelbaum, Michael Toce, Laura Tormoehlen, Andrew Troger, David Vearrier, George Wang, Sam Wang, George Warpinski, Mitchell Waters, Christopher Watson, Mary Wermuth, James Whitledge, Timothy Wiegand, Brian Wolk, David Wood, Mark Yarema, Luke Yip, Amy Young, Matthew Zuckerman

Author Contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Alexandra Amaducci, Sharan Campleman, Shao Li, Kim Aldy, Dana Karshenas, and Rachel Culbreth. The first draft of the manuscript was written by Alexandra Amaducci and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding The Toxicology Investigators Consortium Core Registry received partial funding through licensing agreements with the Centers for Disease Control and Prevention (75D30120C07819), U.S. Food and Drug Administration (75F40122D00028), BTG International, Inc. (North America), and through grants from the American Academy of Addiction Psychiatry (1H79TI085588) and the National Institute on Drug Abuse (Mt. Sinai; 5R01DA048009 and CDC Supplement R01DA048009-03S1).

Data Availability Data are available upon request on a case-by-case basis.

Declarations

Conflict of Interest AMA, SLC, SL, MBS, LAF, AMK, RC, PMW, JB, KA: These authors have no conflicts of interest to report.

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