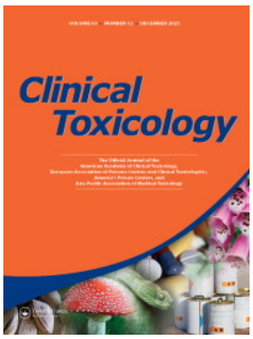

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POISON CENTRE RESEARCH



# Trends in nitrous oxide abuse and misuse: a 22-year analysis of United States poison center data

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**ABSTRACT**

**Introduction:** Nitrous oxide is widely available for medical, industrial, and culinary use. However, its euphoric effects and accessibility have contributed to increasing recreational abuse/misuse. Chronic exposure disrupts vitamin $B_{12}$ function, resulting in potentially severe neurologic and psychiatric complications. Although case reports suggest a rise in abuse/misuse, trends in the United States remain poorly characterized.

**Methods:** We conducted a retrospective analysis of intentional nitrous oxide abuse/misuse reported to the National Poison Data System® from 2003 through 2024. Included cases involved individuals aged 13 years and older, in whom nitrous oxide was identified as the primary substance. Data were analyzed for demographic characteristics, clinical effects, treatments, and outcomes using standardized coding definitions.

**Results:** Of 3,632 cases initially identified, 1,751 met the inclusion criteria. Most were male (63%), and most exposures occurred in private residences (85%). Individuals aged 20–29 years accounted for the largest proportion (37%) of cases. Annual cases rose from 28 in 2003 to 401 in 2024, a 1,332% increase. Over half (55%) of the exposures resulted in the moderate or major clinical effects, including ataxia (11%), numbness (12%), and confusion (14%). Hospital admission occurred in 29% of cases, with 10% admitted to the intensive care unit. Vitamin $B_{12}$ and folate supplementation were documented in only 6.3% of cases.

**Discussion:** These findings demonstrate a sustained and substantial increase in reported intentional nitrous oxide abuse/misuse over two decades in the United States, with a notable rise in cases involving neurologic injury and functional impairment. The high proportion of single-substance exposures and limited use of targeted treatment suggest underrecognition of both the diagnosis and its potential severity. Emerging formulations, including flavored high-volume tanks, may be contributing to this trend.

**Conclusions:** Intentional nitrous oxide abuse/misuse reported to United States poison centers has risen sharply in both frequency and severity in the United States. Improved clinical awareness, regulatory oversight, and public health interventions are needed to address this growing toxicologic concern.

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Deficiency; inhalant abuse and misuse; nitrous oxide; peripheral neuropathy; subacute combined degeneration; vitamin $B_{12}$

## Introduction

Nitrous oxide is a widely available inhalational anesthetic and food additive legally used in products such as whipped cream dispensers. Accessibility and euphoric effects have contributed to its widespread abuse/misuse, particularly among adolescents and young adults. Nitrous oxide cartridges, often referred to as "whippets," are easily obtained over the counter, facilitating recreational use due to their accessibility and rapid onset [1–3].

Nitrous oxide exerts its toxicity by oxidizing the cobalt ion within cobalamin, irreversibly inactivating methylcobalamin. This inactivation blocks methionine synthase, a key enzyme in one-carbon metabolism that remethylates homocysteine to methionine, leading to accumulation of homocysteine, depletion of methionine and S-adenosylmethionine, and impaired methylation essential for myelin integrity. Functional cobalamin deficiency also compromises adenosylcobalamin, the cofactor for methylmalonyl-CoA mutase, resulting in accumulation of methylmalonic acid [4]. These biochemical changes cause neuronal demyelination and subacute combined degeneration of the spinal cord [3,4]. Unlike classic nutritional vitamin $B_{12}$ deficiency, nitrous oxide toxicity often presents with neurotoxicity (paresthesia and ataxia), without hematologic abnormalities such as macrocytosis or anemia [5].

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While several case series have described nitrous oxide-related toxicity in the United States (US), few larger cohort studies or systematic reviews exist [6–8]. This study characterizes trends in the abuse/misuse of nitrous oxide reported to US poison centers over 22 years, detailing demographic characteristics, clinical effects, and outcomes.

## Methods

We conducted a retrospective study of intentional nitrous oxide abuse/misuse exposures in patients aged 13 years and older reported to the National Poison Data System® (NPDS®) from 1 January 2003 through 31 December 2024. The NPDS®, maintained by America's Poison Centers®, aggregates data from 55 US poison centers, which provide toxicology consultation to the public and healthcare professionals. Specialists in poison information collect and code exposure data in real time.

We received de-identified NPDS® data for all intentional misuse or abuse cases in individuals aged 13 years and older. "Intentional misuse" is defined as an exposure due to intentional, improper, or incorrect use of a substance for reasons other than the pursuit of psychotropic effect. "Intentional abuse" is defined as an exposure from the intentional, improper, or incorrect use of a substance in which the patient was likely attempting to gain a "high," euphoric effect, or some other psychotropic effect, including recreational use of a substance. Only coded data were provided for analysis; free text fields and cases with missing age data were excluded. Data included both single-substance and polysubstance exposures. Clinical effects were coded by trained poison information specialists based on reported symptoms from caller reports or clinician reports. Outcomes were coded according to the NPDS® coding manual [9]: no effect, minor effect, moderate effect, major effect, or death. Minor effects are defined as self-limited, whereas moderate and major effects involve clinically significant or life-threatening symptoms.

We implemented segmented regression on monthly exposure counts to estimate the inflection point of exposure increase. Secondary analysis of de-identified data was deemed exempt by the institutional review board.

## Results

Between 2003 and 2024, US poison centers recorded 3,632 cases of intentional nitrous oxide abuse/misuse in individuals aged ≥13 years old. Of these, 2,317 involved nitrous oxide as the primary substance. After excluding 166 confirmed non-exposures and 400 cases with unknown outcomes, 1,751 were included in the final analysis (Figure 1).

The highest proportion occurred among 20–29-year-olds (36.8%; $n=645$), followed by 30–39-year-olds (24.4%; $n=427$) and adolescents aged 13–19 years (16.9%; $n=296$). Males comprised 62.8% ($n=1,100$) of cases, females 36.9% ($n=646$), and gender was unspecified in 0.3% ($n=5$). Most were classified as abuse (92.9%; $n=1,626$), with only 7.1% ($n=125$) classified as misuse (Table 1).

Single-substance exposures accounted for 83.4% ($n=1,461$), while 16.6% ($n=290$) involved multiple substances. The most frequent co-exposures were ethanol 5.7% ($n=99$), cannabis 2.6% ($n=46$), and benzodiazepines 2.2% ($n=38$) (Table 2).

Annual cases increased from 28 in 2003 to 401 in 2024, a 1,332% rise. Between 2020 and 2024, cases increased 360% (87 to 401), with a 112% increase from 2023 to 2024. Moderate/major outcomes rose from eight cases in 2003 to 237 in 2024. Minor/no-effect cases rose from 20 to 164. Overall, 55.1% ($n=966$) had moderate/major/fatal outcomes, and 44.8% ($n=785$) had minor or no effects (Figure 2).

The clinical effects associated with nitrous oxide abuse/misuse were diverse, most commonly neurological. Among reported cases, 12% ($n=210$) reported numbness, 10.9% ($n=191$) reported ataxia, 9.5% ($n=166$) reported peripheral neuropathy, and 9.3% ($n=163$) reported weakness. Tachycardia occurred in 13.6% ($n=239$), and "other neurologic" in 10.8% ($n=189$).

The most common treatment was "other" (unspecified), accounting for 25.5% ($n=446$). Intravenous fluids were administered in 20.4% ($n=357$) of cases, while fresh air administration and supplemental oxygen were administered in 8% ($n=140$) and 11% ($n=193$), respectively. Fresh air administration refers to moving symptomatic patients to a well-ventilated environment. Benzodiazepines were used in 10.1% ($n=177$) of cases, and other sedatives in 3.4% ($n=60$). Folate was given in only 4.3% ($n=75$) of cases, and hydroxocobalamin (no specified route) in 2.3% ($n=40$), and methionine was not documented as given in any cases. Endotracheal Intubation was performed in 3.2% ($n=56$).

Critical care admissions occurred in 10.3% ($n=181$) and 19.2% ($n=336$) were admitted to non-critical care units. About 50% ($n=876$) were treated and discharged, 4.5% ($n=78$) left against medical advice or were lost to follow-up, and psychiatric facility admissions occurred in 5.1% ($n=89$) of cases. The remaining cases had unknown outcomes or did not arrive at a

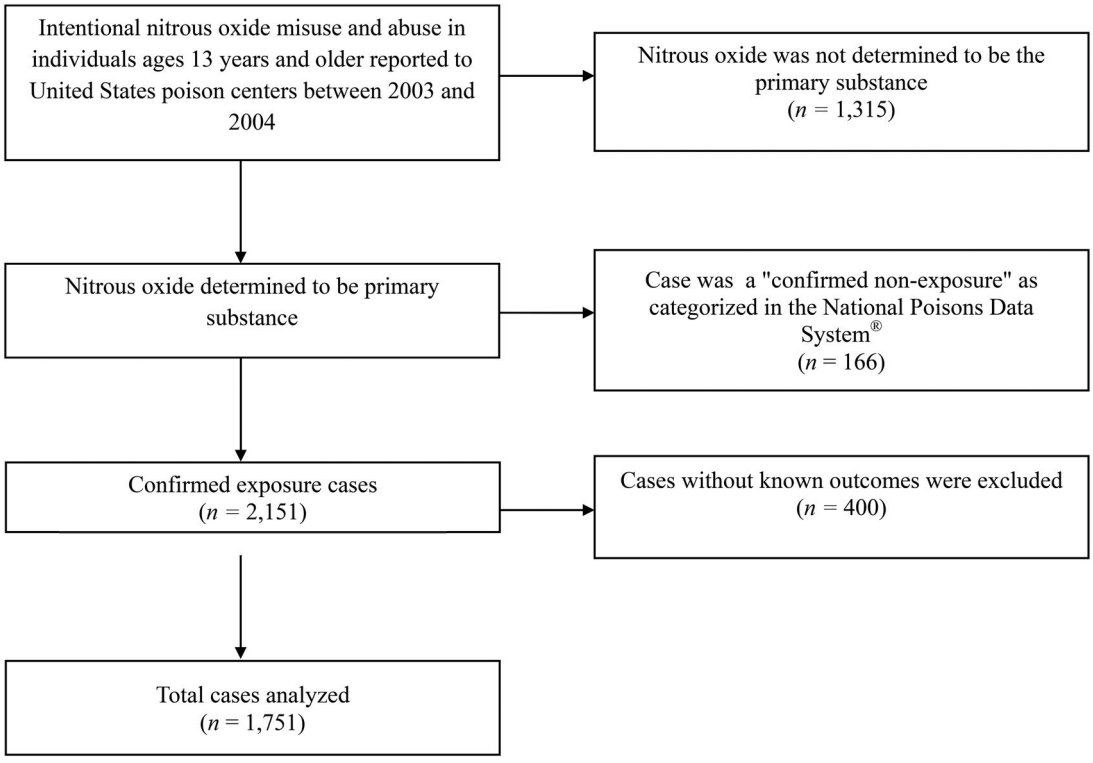


**Figure 1.** Inclusion and exclusion flow chart of intentional nitrous oxide misuse and abuse cases in individuals aged 13 years and older reported to United States poison centers between 2003 and 2024. Of 3,632 cases identified, exclusions were applied for non-primary substance involvement, confirmed non-exposure, and cases without known outcomes, resulting in 1,751 total cases analyzed.

healthcare facility. Rehabilitation or physical therapy data were unavailable.

Most exposures occurred at the patient's residence (84.8%; $n=1,485$), followed by public areas (2.2%; $n=38$) and other residences (1.9%; $n=33$). Workplace exposures accounted for 1% ($n=18$), while 7.1% ($n=124$) were unknown locations.

We fit the monthly count of exposures over time ($n=254$ months) using a segmented regression and found a highly significant ($P<0.001$) inflection point at January 2023 (month 200; 95% CI: 193 to 207 months; June 2022 to August 2023). At this inflection point, the relationship between time and count of exposures changed from static to approximately exponential (Figure 3).

Cases were distributed relatively evenly across days of the week (209–268 cases per day). The mean daily number of exposures ranged from four to five, and no statistically significant day-of-week variation was identified. Cases occurred throughout all seasons with no major differences in distribution. The total number of cases ranged from 396 (18.5%) in winter to 468 (21.3%) in summer, with intermediate values in spring (20.6%) and fall (19.7%). Mean seasonal counts ranged between 18 and 21 cases yearly.

## Discussion

Over the past two decades, intentional nitrous oxide abuse/misuse reported to US poison centers has risen sharply, with a >14-fold increase in cases reported to poison centers between 2003 and 2024. This mirrors increasing recreational use among individuals aged 20–29 years, consistent with broader substance-use trends in this group [2,5]. A growing share of exposures resulted in moderate or major clinical effects, underscoring an escalation in severity. Neurologic symptoms (ataxia, numbness, and peripheral neuropathy) were most common, aligning with the known neurotoxicity of nitrous oxide.

Although subacute combined degeneration of the spinal cord is the classic manifestation of nitrous toxicity, the clinical spectrum is broader, encompassing a range of peripheral, psychiatric, and hematologic manifestations that reflect its larger impact on cobalamin-dependent pathways. Persistent neuropathies may occur despite vitamin $B_{12}$ repletion [10,11]. Agbo et al. [12] found that nitrous oxide-related cases showed more severe neurologic and psychiatric symptoms than those from vitamin $B_{12}$ deficiency alone, suggesting direct neurotoxicity beyond $B_{12}$ inactivation.

**Table 1.** Demographic characteristics presented for the most common and clinically notable findings, including age distribution, gender, site and route of exposure, intent, management site.

| Parameter | All exposures ($n = 1,751$) *n* (%) | Outcome: moderate, major, death ($n = 966$) *n* (%) | Outcome: minor or no effect ($n = 785$) *n* (%) |
|---|---|---|---|
| **Age** | | | |
| 13–19 years | 296 (16.9) | 128 (13.3) | 168 (21.4) |
| 20–29 years | 645 (36.8) | 359 (37.2) | 286 (36.4) |
| 30–39 years | 427 (24.4) | 246 (25.5) | 181 (23.1) |
| 40–49 years | 208 (11.9) | 138 (14.3) | 70 (8.9) |
| 50-59 years | 95 (5.4) | 61 (6.3) | 34 (4.3) |
| >60 years | 34 (1.9) | 23 (2.4) | 11 (1.4) |
| Unknown | 46 | 11 | 35 |
| **Gender** | | | |
| Male | 1,100 (62.8) | 612 (63.4) | 488 (62.2) |
| Female | 646 (36.9) | 353 (36.5) | 293 (37.3) |
| Unknown | 5 | 1 | 4 (0.5) |
| Single-substance exposure | 1,461 (83.4) | 762 (78.9) | 699 (89.0) |
| **Exposure site** | | | |
| Own residence | 1,485 (84.8) | 824 (85.3) | 661 (84.2) |
| Public area | 38 (2.2) | 20 (2.1) | 18 (2.3) |
| Other residence | 33 (1.9) | 11 (1.1) | 22 (2.8) |
| Workplace | 18 (1.0) | 10 (1.0) | 8 (1.0) |
| Other | 53 (3.0) | 29 (3.0) | 24 (3.1) |
| Unknown | 124 | 72 | 52 |
| **Caller site** | | | |
| Health care facility | 1,479 (84.5) | 895 (92.7) | 584 (74.4) |
| Own residence | 191 (10.9) | 43 (4.5) | 148 (18.9) |
| Other residence | 12 (0.7) | 5 (0.5) | 7 (0.9) |
| Workplace | 9 (0.5) | 3 (0.3) | 6 (0.8) |
| Other | 49 (2.8) | 16 (1.7) | 33 (4.2) |
| Unknown | 11 | 4 | 7 |
| **Route of exposure** | | | |
| Inhalation | 1,606 (91.7) | 892 (92.3) | 714 (91.0) |
| Ingestion | 130 (7.4) | 66 (6.8) | 64 (8.2) |
| Dermal | 9 (0.5) | 4 (0.4) | 5 (0.6) |
| Other | 2 (0.1) | 1 (0.1) | 1 (0.1) |
| Unknown | 4 | 3 | 1 |
| **Reason for exposure** | | | |
| Intentional–abuse | 1,626 (92.9) | 927 (96.0) | 699 (89.0) |
| Intentional–misuse | 125 (7.1) | 39 (4.0) | 86 (11.0) |
| **Management site** | | | |
| Patient already in (en route to) health care facility when poison center called | 1,490 (85.1) | 907 (93.9) | 583 (74.3) |
| Managed on site (non-health care facility) | 156 (8.9) | 16 (1.7) | 140 (17.8) |
| Patient was referred by poison center to a health care facility | 88 (5.0) | 38 (3.9) | 50 (6.4) |
| Other | 11 (0.6) | 3 (0.3) | 8 (1.0) |
| Unknown | 6 | 2 | 4 |
| **Level of health care facility care** | | | |
| Admitted to critical care unit | 181 (10.3) | 163 (16.9) | 18 (2.3) |
| Admitted to non-critical care unit | 336 (19.2) | 278 (28.8) | 58 (7.4) |
| Admitted to psychiatric facility | 89 (5.1) | 44 (4.6) | 45 (5.7) |
| Patient lost to follow-up/left against medical advice | 78 (4.5) | 34 (3.5) | 44 (5.6) |
| Patient refused referral/did not arrive at health care facility | 18 (1.0) | 3 (0.3) | 15 (1.9) |
| Treated/evaluated and released | 876 (50.0) | 423 (43.8) | 453 (57.7) |
| Unknown | 173 | 21 | 152 |

Psychiatric and cognitive symptoms (including depression, psychosis, and executive function deficits) are increasingly recognized [13]. These effects can persist beyond acute intoxication, with neuroimaging suggesting possible long-term structural or functional changes [14,15]. Some patients present with isolated psychiatric features such as paranoia or hallucinations, delaying diagnosis [16]. Recent reviews identified hallucinations, agitation, and cognitive slowing as underreported but recurrent findings, particularly in adolescents [13,17].

Interestingly, clinical severity varies substantially between individuals, despite a consistent underlying biochemical mechanism involving functional vitamin $B_{12}$ inactivation. While many remain asymptomatic, others experience debilitating neurologic or psychiatric symptoms. This variability may reflect involvement of additional factors such as preexisting nutritional

**Table 2.** Co-exposures, major neurologic, respiratory, cardiovascular, and laboratory effects, as well as therapies administered among reported cases ($n = 1,751$). Variables are defined according to the National Poison Data System®, not all available variables are shown.

| Parameter | All exposures ($n = 1,751$) *n* (%) | Outcome: moderate, major, death ($n = 966$) *n* (%) | Outcome: minor or no effect ($n = 785$) *n* (%) |
|---|---|---|---|
| **Co-exposures** | | | |
| Antihistamines | 7 (0.4) | 6 (0.6) | 1 (0.1) |
| Diphenhydramine | 3 (0.2) | 3 (0.3) | 0 |
| Metamfetamines and/or amfetamines | 19 (1.1) | 14 (1.4) | 5 (0.6) |
| Opioids | 16 (0.9) | 14 (1.4) | 2 (0.3) |
| Marijuana | 46 (2.6) | 32 (3.3) | 14 (1.8) |
| Benzodiazepines | 38 (2.2) | 26 (2.7) | 12 (1.5) |
| Ethanol beverage | 99 (5.7) | 68 (7.0) | 31 (3.9) |
| **Neurologic effects** | | | |
| Ataxia | 191 (10.9) | 169 (17.5) | 22 (2.8) |
| Peripheral neuropathy | 166 (9.5) | 157 (16.3) | 9 (1.1) |
| Muscle weakness | 163 (9.3) | 142 (14.7) | 21 (2.7) |
| Numbness | 210 (12.0) | 156 (16.1) | 54 (6.9) |
| Tremor | 73 (4.2) | 71 (7.3) | 2 (0.3) |
| Confusion | 237(13.5) | 189 (19.6) | 48 (6.1) |
| Dizziness/vertigo | 86 (4.9) | 53 (5.5) | 33 (4.2) |
| Drowsiness/lethargy | 87 (5.0) | 51 (5.3) | 36 (4.6) |
| Hallucinations delusions | 51 (2.9) | 47 (4.9) | 4 (0.5) |
| Headache | 58 (3.3) | 27 (2.8) | 31 (3.9) |
| Agitation | 127 (7.3) | 103 (10.7) | 24 (3.1%) |
| Seizure | 39(2.2) | 39 (4.0) | 0 |
| Slurred speech | 21 (1.2) | 18 (1.9) | 3 (0.4) |
| Syncope | 51 (2.9) | 50 (5.2) | 1 (0.1) |
| Other neurological | 189 (10.8) | 147 (15.2) | 42 (5.4) |
| **Respiratory effects** | | | |
| Bronchospasm | 6 (0.3) | 6 (0.6) | 0 |
| Coughing | 17 (1.0) | 12 (1.2) | 5 (0.6) |
| Dyspnea | 61 (3.5) | 56 (5.8) | 5 (0.6) |
| Esophageal injury | 3 (0.2) | 1 (0.1) | 2 (0.3) |
| Throat irritation | 59 (3.4) | 21 (2.2) | 38 (4.8) |
| Oral burns | 18 (1.0) | 11 (1.1) | 7 (0.9) |
| Oral irritation | 27 (1.5) | 10 (1.0) | 17 (2.2) |
| Oropharyngeal edema | 10 (0.6) | 6 (0.6) | 4 (0.5) |
| Respiratory depression | 37 (2.1) | 36 (3.7) | 1 (0.1) |
| Respiratory arrest | 3 (0.2) | 3 (0.3) | 0 |
| Other respiratory | 20 (1.1) | 18 (1.9) | 2 (0.3) |
| **Cardiovascular effects** | | | |
| Tachycardia | 239 (13.6) | 198 (20.5) | 41 (5.2) |
| Bradycardia | 18 (1.0) | 17 (1.8) | 1 (0.1) |
| Atrial Fibrillation/flutter | 2 (0.1) | 2 (0.2) | 0 |
| Conduction disturbance | 5 (0.3) | 5 (0.5) | 0 |
| Dysrhythmia unspecified | 2 (0.1) | 2 (0.2) | 0 |
| QTc prolongation | 17 (1.0) | 17 (1.8) | 0 |
| QRS complex prolongation | 3 (0.2) | 3 (0.3) | 0 |
| Electrocadiographic changes (other, unspecified) | 9 (0.5) | 9 (0.9) | 0 |
| Hypotension | 37 (2.1) | 36 (3.7) | 1 (0.1) |
| Asystole | 4 (0.2) | 4 (0.4) | 0 |
| Cardiac arrest | 4 (0.2) | 4 (0.4) | 0 |
| Other cardiovascular abnormalities | 10 (0.6) | 7 (0.7) | 3 (0.4) |
| **Laboratory abnormalities** | | | |
| Aspartate/alanine aminotransferase activity 100–999 U/L | 11 (0.6) | 11(1.1) | 0 |
| Aspartate/alanine aminotransferase activity >1,000 U/L | 3 (0.2) | 3 (0.3) | 0 |
| Low hemoglobin concentration | 22 (1.3) | 21(2.2) | 1 (0.1) |
| Methemoglobinemia | 2 (0.1) | 2 (0.2) | 0 |
| **Therapies** | | | |
| Other/miscellaneous | 446 (25.5) | 359 (37.2) | 87 (11.1) |
| Intravenous fluids | 357 (20.4) | 287 (29.7) | 70 (8.9) |
| Oxygen | 193 (11.0) | 159 (16.5) | 34 (4.3) |
| Fresh air | 140 (8.0) | 52 (5.4) | 88 (11.2) |
| Hydroxocobalamin | 40 (2.3) | 33 (3.4) | 7 (0.9) |
| Folate | 75 (4.3) | 67 (6.9) | 8 (1.0) |
| Thiamine | 58 (3.3) | 54 (5.6) | 4 (0.5) |
| Benzodiazepines | 177 (10.1) | 142 (14.7) | 35 (4.5) |
| Sedation, other | 60 (3.4) | 51 (5.3) | 9 (1.1) |
| Cardiopulmonary resuscitation | 11 (0.6) | 11 (1.1) | 0 |
| Hemodialysis | 4 (0.2) | 4 (0.4) | 0 |
| Endotracheal intubation | 56 (3.2) | 55 (5.7) | 1 (0.1) |
| Vasopressors | 22 (1.3) | 22 (2.3) | 0 |
| Mechanical ventilation | 48 (2.7) | 48 (5.0) | 0 |


Figure 2. Annual number of intentional nitrous oxide exposures reported to United States Poison centers from 2003 to 2024 stratified by clinical effect severity.

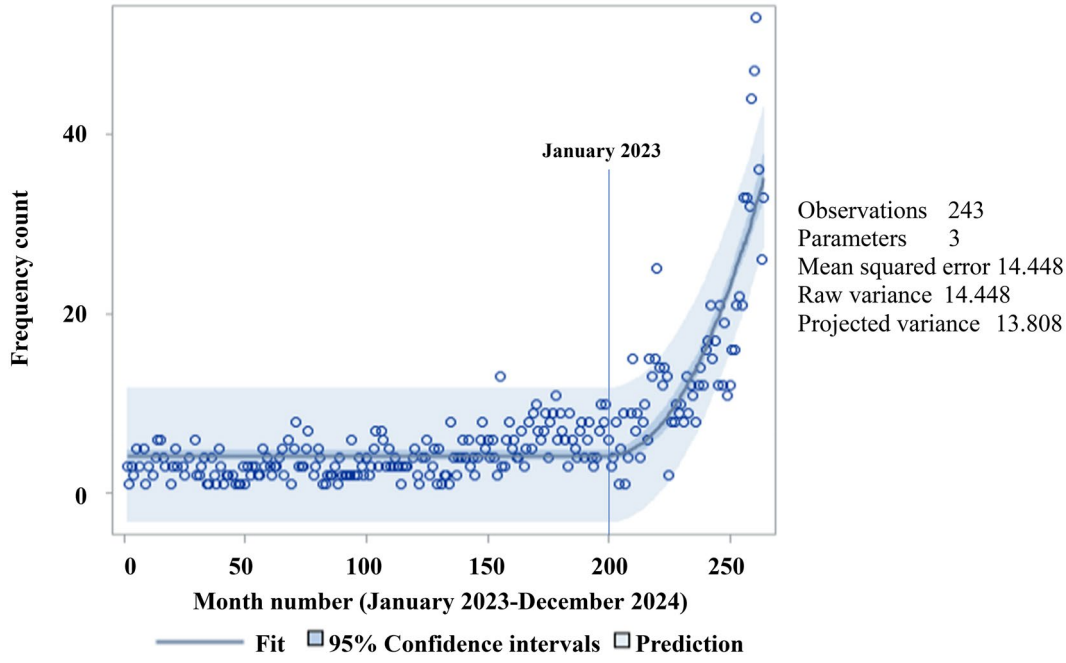


Figure 3. Segmented regression of count of ingestions over time ($n = 254$ months) found a highly significant ($P < 0.001$) inflection point at January 2023 (month 200 [95% CI: 193 to 207 months; June 2022 to August 2023]). At this inflection point, the relationship between time and count of ingestions changed from static to approximately exponential.

deficiencies and genetic susceptibility. Individuals with low baseline vitamin $B_{12}$ or folate concentrations, such as in restrictive diets, alcohol use disorders, or malabsorption syndromes, may have less compensatory reserve for metabolic disruptions caused by nitrous oxide exposure [18]. Genetic polymorphisms in enzymes involved in methylation pathways have been associated with elevated homocysteine concentrations and may increase the risk of neurologic complications and hypercoagulability [19]. In addition to these metabolic vulnerabilities, nitrous oxide also acts as a non-competitive N-methyl-D-aspartate receptor antagonist, disrupting glutamatergic signaling and contributing to dissociative and psychiatric effects [20–22].

Most reported exposures occurred in private residences, highlighting the isolated and concealed nature of use. Supported by international data, this finding suggests that nitrous oxide is often used at home due

to portability and discreet use [5]. Further contributing to this is the availability of purchase through online platforms and major retailers. During the COVID-19 pandemic, nitrous oxide use rose further, likely driven by social isolation, restricted access to other substances, and increased psychological distress among young adults. Several studies have analyzed and validated findings from the Global Drug Survey, showing complex shifts in substance use during the pandemic [23]. While use of classic "party drugs," such as 3,4-methylenedioxymetamfetamine, declined with reduced social opportunities, coping-related use of substances such as benzodiazepines, prescription opioids, and cannabis increased [24]. Motivations also shifted, with many young adults and marginalized groups reporting use linked to stress, boredom, and mental health challenges [25].

These heterogeneous changes, observed in the United States and Europe, are consistent with Global Drug Survey data and underscore the need for targeted prevention and mental health support. In the United Kingdom, survey data specifically indicated a rise in nitrous oxide use among individuals under 25 during lockdown periods [5], and international poison center data reported an increase in neurologic complications associated with use during this period [21,26]. The even more dramatic increase observed in the recent years likely reflects additional factors beyond COVID-19, including the transition from single-use cartridges to large-volume tanks, enhanced availability through online vendors and retail outlets, and marketing strategies that reinforce perceptions of nitrous oxide as a low-risk substance despite its well-documented toxic effects.

The predominance of single-substance exposures (83%) reflects accessibility and perceived safety [5]. However, frequent co-use with alcohol or benzodiazepines warrants vigilance, as polydrug exposures complicate management and outcomes [3]. Public health initiatives targeting young adults, including education and harm-reduction campaigns, are essential [2,27].

Clinical outcomes indicate a substantial healthcare burden: nearly 30% required hospital admission, and 10% required intensive care unit care. Intensive care needs typically stem from severe neurologic impairment, respiratory failure, or autonomic instability. Rarely, extracorporeal membrane oxygenation has been used for nitrous-related pulmonary injury [28,29]. The NPDS® lacks granular data on such interventions, likely underestimating severity.

Delays in diagnosis are common because symptoms are nonspecific and vitamin $B_{12}$ concentrations may appear normal. Up to one-third of affected patients lack hematologic abnormalities [4]. Methylmalonic acid and homocysteine are more sensitive markers [31]. The findings of magnetic resonance imaging may be subtle or missed if imaging excludes thoracic segments [32]. Electromyography and nerve conduction studies can aid diagnosis but are rarely performed acutely [3,30]. Early recognition and prompt vitamin $B_{12}$ replacement remain critical to prevent progression. Although oral and intramuscular vitamin $B_{12}$ are therapeutically equivalent [33], parenteral administration is preferred in severe neurologic cases. Some patients worsen despite supplementation, emphasizing early detection and strict abstinence [34–36]. Concurrent vitamin $B_{12}$ use during ongoing exposure is ineffective [4].

Direct measurement of nitrous oxide in biological samples is not clinically useful because the gas is rapidly cleared within minutes of inhalation, and no validated consumption markers exist. Clinical evaluation should rely instead on effect biomarkers that reflect disruption of vitamin $B_{12}$-dependent pathways. Homocysteine and methylmalonic acid are the most reliable laboratory markers for diagnosis and follow-up, while total serum vitamin $B_{12}$ concentration may be normal despite clinically significant toxicity. Consistent with the prior meta-analytic findings, analysis by Mondesert et al. [37] suggests that reductions in plasma folate and hemoglobin concentrations, and increases in mean corpuscular volume provide the limited additional diagnostic value in this setting. Interpretation requires caution, as folate deficiency and renal impairment can elevate homocysteine and methylmalonic acid independent of nitrous oxide exposure. Holotranscobalamin may detect functional deficiency earlier than the measurement of total vitamin $B_{12}$ concentrations, but it is not widely available and lacks standardized cutoffs in this setting. The plasma methionine concentration may also be reduced, but it is not a validated or specific marker. For follow-up, homocysteine and methylmalonic acid concentrations can be monitored to assess biochemical recovery after cessation of nitrous oxide and vitamin $B_{12}$ replacement [38].

Despite frequent neurologic findings, vitamin $B_{12}$ and folate therapy were rarely documented (hydroxocobalamin 2.3%, folate 4%), and methionine administration was not reported. This likely reflects underrecognition, incomplete documentation, or coding constraints (i.e. documentation under the other/miscellaneous category) rather than lack of treatment. The literature consistently supports early parenteral vitamin $B_{12}$ as the cornerstone of management, with folate as adjunctive therapy. Methionine supplementation is not standard in

the US, though it is occasionally used elsewhere in refractory cases [39,40].

Comparable increases in recreational nitrous oxide use and associated neurologic injury have been reported internationally, with consistent findings from poison centers and clinical cohorts across Europe, Asia, and Australia, underscoring that these trends extend beyond the US [2,5–7,16,17,27,29,30,42]. From a public health perspective, the regulatory response to nitrous oxide misuse remains inconsistent. It is widely available, marketed as a food-grade product with little indication of potential toxicity and limited purchase restrictions [13,27]. Several countries have addressed this gap; while national restrictions have been implemented in the United Kingdom and the Netherlands, the US continues to rely on a fragmented, state-level approach. In the United Kingdom, nitrous oxide was classified as a Class C drug in 2023, criminalizing recreational possession [41]. The Netherlands also banned its commercial trade, adding it to Schedule II of the Dutch Opium Act [42], and Western Australia introduced restrictions on canister sales to reduce nonmedical use [43]. Despite these efforts, nitrous oxide remains widely accessible through retail outlets, convenience stores, 24/7 delivery services, and online platforms, with internet search activity and social media trends suggesting sustained interest. Market observations indicate a shift toward larger-volume cylinders and bulk sales, reflecting evolving distribution patterns [6]. In the US, it is legally accessible for non-recreational purposes, including use by licensed professionals in medical, dental, or surgical settings, as a food-grade propellant, and for industrial or automotive applications. Still, regulation remains limited at the federal level, though some states have enacted legislation. As of 2025, Oregon and New York mandate age verification for nitrous oxide purchases online and in stores [44,45]. Most states do not regulate purchase age, though some, such as Washington, have local ordinances, while others impose restrictions based on quantity or intended use. In Louisiana, a statewide retail ban on nitrous oxide sales was enacted in 2024 to curb misuse [46]. Despite these measures, nitrous oxide remains easily accessible online, and patterns of use among vulnerable populations remain a concern. Most cases of nitrous oxide toxicity are preventable; public health strategies should prioritize clinician awareness, education, harm reduction, and tighter supply regulation while avoiding punitive measures that may stigmatize users or deter care [47]. Co-exposure with ethanol, cannabis, or benzodiazepines may further increase risk, particularly in communities with limited healthcare access.

Improved surveillance could link poison center data with emergency department and rehabilitation records. The French PROTOSIDE network exemplifies such coordination, integrating emergency medicine, neurology, and addiction services to standardize biomarkers and prevention efforts [48]. Similar models could strengthen US toxicovigilance.

The limitations of this study include retrospective design, incomplete follow-up, and underreporting. The NPDS® likely underestimates true incidence since many cases present outside poison center consultation. Variability in clinician reporting and coding practices may affect accuracy and the National Poison Data System® data cannot represent national incidence. Future work should include prospective surveillance and linkage with neurologic outcomes to define recovery better. Despite these limitations, our findings highlight the important national trends in nitrous oxide toxicity.

## Conclusions

Reported nitrous oxide abuse/misuse in the US has increased substantially over the past two decades, with a rise in both frequency and severity of clinical effects. These findings support the need for improved public health surveillance, stronger regulatory oversight, and enhanced clinical education to improve early recognition and management of nitrous oxide related harm. Proactive intervention strategies will be critical to mitigating long-term neurologic and psychiatric consequences in at-risk populations.

## Disclaimer

America's Poison Centers® maintains the National Poison Data System® (NPDS®), which houses de-identified records of self-reported information from callers to the country's Poison Centers. The NPDS® data do not reflect the entire universe of US exposures and incidences related to any substance(s). Exposures do not necessarily represent a poisoning or overdose and America's Poison Centers® is not able to completely verify the accuracy of every report. The NPDS® data do not necessarily reflect the opinions of America's Poison Centers®.

## Disclosure statement

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## Data availability statement

The data that support the findings of this study are available from the corresponding author, CC, upon reasonable request.

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