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Sodium azide poisoning: a narrative review

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Abstract

Context: Sodium azide is a highly toxic chemical. Its production has increased dramatically over the last 30 years due to its widespread use in vehicular airbags, and it is available for purchase online. Thus, accidental exposure to azide or use as a homicidal or suicidal agent could be on the rise, and secondary exposure to medical personnel can occur. No antidote exists for azide poisoning. We conducted a systematic review of azide poisoning to assess recent poisoning reports, exposure scenarios, clinical presentations, and treatment strategies.

Methods: We searched both medical and newspaper databases to review the literature between 01/01/2000 and 12/31/2020, pairing the controlled vocabulary and keyword terms "sodium azide" or "hydrazoic acid" with terms relating to exposures and outcomes, such as "ingestion," "inhalation," "exposure," "poisoning," and "death." We included all peer-reviewed papers and news articles describing human azide poisoning cases from English and non-English publications that could be identified using English keywords. Data abstracted included the number, age, and gender of cases, mode of exposure, exposure setting, azide dose and route of exposure, symptoms, outcome, and treatment modalities.

Results: We identified 663 peer-reviewed papers and 303 newspaper articles. After removing duplicated and non-qualifying sources, 54 publications were reviewed describing 156 cases, yielding an average of 7.8 reported azide poisoning cases per year. This rate is three times higher than in a previous review covering the period of 1927 to 1999. Poisoning occurred most commonly in laboratory workers, during secondary exposure of medical personnel, or from a ripped airbag. Hypotension occurred commonly, in some cases requiring vasopressors and one patient received an intra-aortic ballon pump. Gastric lavage and/or activated charcoal were used

for oral azide ingestion, and sodium nitrite, sodium thiosulfate, and/or hydroxocobalamin were used in severely poisoned patients.

Conclusions: Recent increases in azide poisoning reports may stem from greater commercial use and availability. Treatment of systemic poisoning may require aggressive hemodynamic support due to profound hypotension. Based on mechanistic considerations, hydroxocobalamin is a rational choice for treating azide poisoning.

Keywords

Introduction

Sodium azide (NaN_3) and its conjugate acid, hydrazoic acid (HN_3), are toxic compounds. We refer to both agents generically as "azide." Fortunately, azide poisoning is relatively rare, but this means most medical personnel may have not encountered a case and possess limited knowledge of azide poisoning. This may prove detrimental in a mass casualty event, for example, an industrial accident or terrorist attack. The latter is possible, because sodium azide is easily available through online retailers and NaN_3 is listed as a potential weapon of mass destruction [1,2]. Indeed, azide has been used in several planned and/or executed terrorist attacks [3–7].

Azide has been most notably used as a propellant in vehicular airbags and airplane safety chutes. Following an automobile crash, an igniter generates high temperatures that rapidly decompose NaN_3 into sodium metal and nitrogen gas. Due mainly to its use in airbags, NaN_3 production surged beginning in 1990, and at least 1,000 tons are produced annually [8,9]. The fate of azide pellets in old airbags is generally unknown, posing a potential environmental problem [10–12]. Azide is also used in chemical laboratories to facilitate synthetic reactions, and in biomedical laboratories to inhibit microbial growth.

Within a year of its discovery, azide was shown to be toxic to plants and animals [13]. The mouse LD_{50} is 19 mg/kg by intravenous injection, and the human lethal dose is estimated to be 700 mg total or ~10 mg/kg [14,15]. Humans can be exposed to azide through three major routes: ingestion, transdermal or transmucosal absorption, or inhalation of hydrazoic acid vapors or sodium azide dust particles. At low doses, azide causes dizziness, nausea, vomiting, and restlessness. At high doses, it causes seizures, hypotension, metabolic acidosis, coma, and respiratory failure. Symptoms occur within minutes of exposure.

Azide has several mechanisms of toxicity. At the cellular level, it inhibits mitochondrial cytochrome C oxidase and catalase [16,17]. The former enzyme is part of complex IV in the mitochondrial electron transport chain and the latter enzyme detoxifies hydrogen peroxide to water and oxygen. Thus, azide can reduce ATP synthesis and cause oxidative stress, the latter due both to mitochondrial electron leakage and reduced catabolism of reactive oxygen species. Cyanide also inhibits cytochrome C oxidase, and azide and cyanide are especially toxic to cells with high respiratory rates, such as neurons and cardiomyocytes. At the organismal level, azide is a potent vasodilator and inhibits platelet aggregation, likely *via*

conversion to nitric oxide. Azide generates nitric oxide *in vitro* in erythrocytes, platelets, and isolated blood vessels, and recently, nitrosyl-hemoglobin was found in the blood of mice that had received azide [18]. Cytochrome C oxidase inhibition and nitric oxide generation likely underlie the hypotension, myocardial and respiratory failure, and metabolic acidosis that occur in azide poisoning.

A previous systematic review examined human azide poisonings between 1927 and 1999 [14]. Due to the marked increase in azide production over the last 30 years and the potential of new treatments, we thought it timely to perform an updated review of human azide poisoning, concentrating on contemporary exposure settings, clinical presentations, and treatment.

Methods

Search strategy

We conducted the study in accordance with the Preferred Reporting Item for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We searched all publications from January 1, 2000 to December 31, 2020 that described human cases of azide exposure and toxicity. We conducted separate searches of peer-reviewed papers and newspaper articles.

KH led the literature searches. For peer-reviewed papers, we searched PubMed (pubmed.gov), Embase (embase.com), and Academic Search Complete (ProQuest) using "sodium azide" and "hydrazoic acid' as controlled vocabulary and keyword terms, pairing them with terms relating to exposure, settings, or outcomes, such as "ingestion," "inhalation," "exposure," "poisoning," and "death." For news articles, we searched Access World News and U.S. Major Dailies using a similar search strategy and keywords, without a controlled vocabulary. Full search strategies for all databases are in Appendix 1. Supplemental Google searches were conducted for both peer-reviewed papers and newspaper articles using the same search terms. All records were imported into EndNote and de-duplication followed the Wichor Bramer process [19].

Inclusion and exclusion criteria

All articles describing human azide exposure were included. Reports of physical trauma due to airbag deployment alone were excluded as were articles on azides other than sodium, since NaN_3 is the principal azide species produced and it is available for purchase online [2,20,21]. Finally, we excluded articles that were duplicated cases, had insufficient data, or irrelevant account, such as no discussion of human azide poisoning.

JT and SS evaluated the titles and abstracts, and full-text of the articles, with GRB arbitrating conflicts. To increase the international scope and relevance, non-English publications were included, when English language search terms led to their identification. If an English translation was unavailable, native language speakers translated appropriate sections of the papers.

Data collection

JT and SS abstracted the following data, when available: the number, age, and gender of cases, mode of exposure (accident, suicide, or homicide), exposure setting (automobile accident, or industrial, laboratory, or secondary exposure of medical personnel), azide dose received and route of exposure (ingestion, inhalation, or dermal contact), clinical symptoms, outcome including hospitalization and survival of the victim(s), and treatment modalities. The level of evidence for each article was determined. If a case was reported in both a peer-reviewed paper and a news article, only the peer-reviewed paper is included.

Results

For peer-reviewed papers, the initial search identified 663 publications. Based on the Wichor Bramer process, 175 duplications were removed. Of the remaining 488 papers, we excluded 432 after screening the titles and abstracts and finding the same case published in multiple journals, or absence of reference to human exposure. We performed full-text review of the remaining 56 eligible papers, excluding an additional 19 papers based on grounds of duplication, irrelevant account, and/or insufficient data. Thus, 37 papers met our inclusion criteria and were reviewed (Figure 1). Among the 37 papers, a native Chinese speaker reviewed one Chinese paper, and a native Japanese speaker (SS) reviewed two Japanese papers.

For news articles, the initial search identified 303 articles. Applying the same screening methods as for the peer-reviewed papers, we removed 133 duplications, and then excluded 107 articles after screening the titles and abstracts. Of the remaining 63 articles eligible for full-text review, 46 articles were excluded, producing 17 news publications that met our inclusion criteria (Figure 2).

Cases are grouped based on the mode of azide exposure, accidental, intentional (suicidal or homicidal), secondary, or unknown, and sub-grouped based on exposure setting. We found a total of 156 unique cases: 106 cases in the 37 peer-reviewed papers (Table 1), and 50 cases in the 17 news articles (Table 2). Of the 37 peer-reviewed papers, 36 were case reports that met level VII evidence: opinions of authorities and/or reports of expert committees, and, one was an observational study that met level IV evidence [22,23]. We did not perform quantitative bias analysis on these publications, because no quantitative data were available in either the peer-reviewed papers or the news articles that would allow us to correlate outcome to exposure location, route, or mode or treatment modalities. The median age of the patients was 32 with a range of 18 to 73 years old. The gender distribution was about 17% females and 31% males, with 52% unknown.

Accidental exposure to azide

In 77 cases, victims were accidentally exposed to NaN_3, either from airbag deployment after a vehicular accident, or in an industrial, laboratory, or medical setting. Three victims died.

Airbag deployment: peer-reviewed papers

In 13 patients, azide exposure occurred from airbag deployment (Table 1(A-1) [9,24–33]). The patients developed symptoms after either inhaling or having dermal or ocular contact with undecomposed NaN_3 released when an airbag ripped during a vehicular accident. Seven people had chemical burns and one person was diagnosed with contact dermatitis [24–27,31,33]. Five patients without prior history of respiratory disease developed pulmonary symptoms such as dyspnea or stridor, and two were diagnosed with chemical pneumonitis [9,28–30,32]. Three patients sustained ocular injury [9,31,32].

Industrial exposure: peer-reviewed papers

Three papers described 43 patients who were accidentally exposed to azide at work, presenting symptoms ranging from mild to severe, including one death (Table 1(A-2) [34,35,36]). One paper was a case-control survey of 41 workers who consistently inhaled more than the legal limit of $0.3mg/m^3$ of NaN_3 over a five-year period. The case subjects reported more events of burning eyes, dizziness, headache, and palpitations than control subjects [34]. In the second paper, a patient working in a poorly ventilated NaN_3 packing factory was hospitalized for diplopia, dizziness, paresthesias, and severely reduced muscle strength that immobilized him for three months [35]. He partially recovered muscle strength, but was left with moderate neurological dysfunction. The last paper described a patient who sustained third-degree burns when his forklift accidently struck a 50-gallon barrel containing NaN_3 waste, resulting in an explosion [36]. He subsequently developed hypotension and metabolic acidosis, and died, likely from both the azide exposure and the severe burns.

Industrial exposure: news articles

A worker died in an industrial explosion. He was cleaning out a filter drum used to produce NaN_3 when the drum exploded, causing burns to >15% of his body (Table 2(A-1) [37]). Less than five years earlier, another azide-induced explosion at the same plant injured four workers, one of whom died [38].

Laboratory exposure: peer-reviewed paper

A chemist was exposed to the equivalent of 13 g (185 mg/kg) of azide while performing an experiment using NaN_3 that led to an explosion (Table 1(A-3) [39]). He suffered thermal and chemical burns and lacerations. On hospitalization, he rapidly deteriorated with profound hypotension. He survived, but his left hand required amputation. Again, his clinical presentation was likely secondary to the combination of azide poisoning and severe burns.

Laboratory exposure: news articles

Six articles described 16 cases of accidental exposure among laboratory workers (Table 2(A-2) [40–45]). A clinical immunology technician dropped a 200-mL bottle containing a weak solution of NaN_3 that generated volatile HN_3. Out of concern, 11 workers were hospitalized but subsequently returned to work without complications [40]. The other five cases involved chemists and were less benign. A graduate student did not follow proper safety procedures, and ingested an azide solution; he became ill, but survived [44]. In four cases, chemical reactions with NaN_3 resulted in explosions, leaving the operators with

superficial burns and minor lacerations. Three explosions were caused by negligence using azide amounts that exceeded safety limits [41,43,45].

Exposure in a medical facility: peer-reviewed papers

Two papers described accidental azide ingestion in a medical facility (Table 1(A-4)). In one case, a dentist ingested ~10 mg NaN_3. At this low dose, she experienced generalized seizures, headache, and vomiting within minutes [46]. In the second case, a hospitalized patient drank a solution containing 1 g NaN_3 that was meant as a urine preservative [47]. She quickly developed generalized seizures, hypotension, and metabolic acidosis. Both patients survived, likely due to a relatively low azide dose in the first case and a rapid and aggressive medical response in the second case.

Exposure in a medical facility: news article

A patient died after swallowing an azide tablet thought to be a painkiller (Table 2(A-3) [48]). He started vomiting and rapidly deteriorated 30 min after ingesting the tablet, and died the next day. The source of the azide tablet was unknown.

Intentional exposure to azide

We found 24 cases of suicidal ingestion of NaN_3 (Tables 1(B-1), 1(B-2), and 2(B)). Thirteen cases occurred inside a laboratory (Table 1(B-1)). We also found four cases of homicidal exposure to NaN_3 (Table 2(C)). Of these 28 cases, 19 of the patients died.

Suicide in a laboratory setting: peer-reviewed papers

Of 13 people who intentionally ingested NaN_3, two were found dead, and the remaining 11 were hospitalized, of whom six later died, leaving five survivors (Table 1(B-1) [49–60]). Many of the patients were hypotensive with metabolic acidosis, consistent with high-dose azide exposure. When the amount of ingested azide could be identified, the highest survivable dose was 1.38 g (patient's weight was unknown) [60].

Suicide in a non-laboratory setting: peer-reviewed papers

Of six cases of suicidal ingestion of NaN_3, two of the patients were found dead (Table 1(B-2) [2,61–65]). The remaining four patients were hospitalized, and three died, of whom two were hypotensive and two had metabolic acidosis. The one surviving patient was particularly notable: a 69 year-old female who ingested ~5 g of NaN_3, about 20-fold more than the estimated lethal human dose, was not hypotensive but had reduced myocardial contraction with a left ventricular ejection fraction of 30% that returned to normal three weeks later [63].

Suicide in a non-laboratory setting: news articles

Five people who ingested NaN_3 in a non-laboratory setting all died, three were found dead, while the other two died after hospitalization (Table 2(B) [66–70]). In one case, NaN_3 was found in the victim's car, but it was unclear if he died due to ingesting azide or inhaling hydrazoic acid, which could have been created by mixing NaN_3 with water [70].

Homicides: news articles

Two articles described four homicidal cases (Table 2(C)). A chemist hoping to cause workplace havoc poisoned three of his colleagues' coffee with ~20 g of NaN_3 [71]. Due to an unusual smell, the victims immediately spat out the coffee, but two of them became mildly ill and the third fell unconscious. In the fourth case, a woman bought NaN_3 to poison her husband to claim his life insurance policy [72]. She also stabbed and bludgeoned him. It was unclear how much azide contributed to his death, but it was found in his blood.

Secondary occupational exposure of medical personnel

We found 29 cases of medical personnel becoming secondarily poisoned while treating azide-poisoned victims. All of the personnel lived.

Secondary exposure of medical personnel: peer-reviewed papers

Ten medical workers were likely exposed to azide from a suicidal patient who was not decontaminated prior to hospitalization (Table 1(C) [58]). Three non-hospital staff who either provided prehospital care or transported the patient to the hospital were admitted to the emergency room for evaluation and were subsequently discharged, presumably without symptoms. But, of seven hospital personnel who were in direct care of the patient, two required time off. One person took a day off on supervisory advice to rest due to fatigue. The second person required several weeks off due to psychological stress from exposure to a toxic chemical. In a separate incident, six hospital personnel likely inhaled HN_3 gas liberated while performing gastric lavage on patients who had drank an azide-poisoned beverage at work (Table 1(C) [73]). They developed ocular irritation, dizziness, dyspnea, and headache, symptoms consistent with low-dose azide exposure, but promptly recovered.

Secondary exposure of medical personnel: news articles

Thirteen medical workers were secondarily exposed (Table 2(D) [42,67,68,70]). One case was particularly notable: a firefighter had to be treated for facial and eye burns after responding to an azide-related university laboratory explosion [42]. Although he was wearing a protective face mask, it was postulated that azide powder contacted his face above the mask, where it reacted with sweat that then dripped down onto his eye.

Unknown exposure

Peer-reviewed papers—Seven workers had to be hospitalized after becoming ill from drinking tea or coffee made from azide-contaminated water, and five people at a restaurant drank azide-tainted iced-tea (Table 1(D) [73,74]). Symptoms occurred within minutes, which included arrhythmias, headache, and hypotension. There were no fatalities.

News articles—A total of 10 people at two different medical schools drank from an azide-tainted coffee pot or coffee machine (Table 2(E) [75,76]). All of the victims survived, although they reported symptoms consistent with low-dose azide exposure.

Treatment

No specific azide antidote currently exists. Therefore, treatments were largely supportive and in response to symptoms. Gastric lavage, with or without activated charcoal, was used in 13 patients, one of whom died [46,47,50,54,55,63,73]. The NaN_3 dose in these cases ranged from 0.1 g to 1.38 g, with the outlier being the one patient who survived 15 g [63].

Twenty-three patients presented with hypotension [2,36,39,47,53,54,57–60,64,73,74]. They received intravenous fluids and/or vasopressors, with some patients requiring large amounts of fluids, e.g., up to 32 L over 12 h [36]. The hypotension was presumably secondary to azide conversion to nitric oxide. Fifteen patients presented with metabolic acidosis, likely due to profound hypotension and anaerobic metabolism to compensate for mitochondrial inhibition [2,36,47,49,50,52–55,57–60,63]. In some cases, acidosis was severe enough that sodium bicarbonate was administered [36,50,53,54]. Two patients underwent hemodialysis, one of whom required an intra-aortic ballon pump to maintain blood pressure; both patients survived [47,60]. One patient who underwent exchange transfusion died [53].

Due to mechanistic similarities between azide and cyanide, many patients were given cyanide antidote(s). Ten patients were treated with sodium thiosulfate, amyl nitrite, and/or sodium nitrite, of whom two died [52,53,73]. One patient treated with hydroxocobalamin survived [57].

Persons who had respiratory distress due to inhaling hydrazoic acid or sodium azide dust were treated with corticosteroids and β-agonists [28,29]. People who had azide contact to skin or eyes received general treatment for a chemical exposure, which included steroids and antibiotics [9,24–27,31–33].

Discussion

We found 156 cases in 37 peer-reviewed papers and 17 news articles over the 20-year period between 2000 and 2020, providing a mean of 7.8 cases per year. For comparison, Chang and Lamm found 185 cases over a 72-year period, or an average of 2.6 cases per year. Our rate could be higher due to better reporting and/or more cases, the latter presumably because of greater azide production in the last 30 years and/or the ease of purchasing sodium azide online.

In the Chang and Lamm review, three people were exposed to sodium azide in vehicular accidents. We found 13 people exposed to sodium azide during airbag deployment. The increase in reported cases is likely because all automobiles sold in the U.S. after September 1, 1998 had to have airbags around the front seat. Five persons developed respiratory symptoms after airbag deployment. These five cases are consistent with reports that both sodium azide and hydrazoic acid can cause respiratory distress in animals [15]. Although azide was the likely cause of the respiratory problems, airbags contain other substances such as talcum powder, sodium carbonate, and sodium hydroxide that could cause pulmonary injury. Seven patients exposed to azide during airbag deployment had evidence of dermal burns and three of the patients had evidence of ocular injury. Even though many airbag manufacturers have stopped using azide, it still persists in airbags in many cars; thus,

physicians need to be aware of potential respiratory, cutaneous, and ocular injuries due to azide exposure from airbag deployment.

Accidental industrial exposure to azide is almost inevitable, since numerous factories either produce sodium azide, or use it in manufacturing processes. Two of the 44 cases of industrial exposure died from azide-related explosions. Azide is shock-sensitive, and vibrations occurring when azide-containing drums were moved may have led to the explosions. Several patients developed neurological symptoms, and neurotoxicity secondary to azide exposure has occurred in other human cases and in animal models [77,78]. Care should be taken to minimize azide inhalation through use of face coverings and working in well-ventilated spaces, as well as minimizing mechanical friction that could trigger azide explosions.

Azide-related laboratory accidents occurred in 17 cases. Several cases seem to have been the result of safety negligence. While no death occurred, several victims sustained serious injury, highlighting the need to be vigilant when working with azide.

Three cases of accidental azide ingestion occurred in a medical facility; one of whom died. Sodium azide is an ordinary white powder that when dissolved in water, becomes a clear, odorless solution. It is thus possible that sodium azide could be confused as medicine and that azide solutions could be mistaken for drinking water. While accidental ingestion of azide in a medical facility is rare, azide is commonly used as a preservative, and its use must be monitored closely.

Chang and Lamm reported azide was used as a suicidal agent by 13 people, all of whom died. We found 24 suicidal cases, of whom 18 died. Death due to azide is dependent on dose and the time between exposure and treatment onset. The latter parameter was impossible to ascertain in many cases. Thirteen of the 24 cases were scientific workers who ingested azide in their laboratories and likely had direct access to the chemical. This, in conjunction with 17 cases of accidental laboratory exposure to azide, indicates laboratory workers constitute a high-risk group with regards to azide poisoning.

We found four attempted homicides using azide. Three cases were laboratory workers who did not sustain serious injury. In another incident, the victim was poisoned by his wife who purchased azide online. These cases highlight the danger of azide in the hands of those with malicious intentions.

Our findings reveal medical personnel are at high risk for azide exposure, 29 people became secondarily poisoned while caring for azide-poisoned patients. Although the risk of serious injury is low, several providers reported dizziness, dyspnea, headache, ocular irritation, and fatigue, symptoms compatible with low dose azide exposure. Medical response personnel need to be aware of the consequences of azide poisoning, both in caring for azide-poisoned victims and to protect themselves from secondary exposure.

Twenty-two people were poisoned after drinking from communal beverage sources. While no long-term sequalae occurred due to low exposure dose and rapid care, it was unclear if the poisoning events were accidental or intentional. The latter highlights the potential threat

of large-scale azide exposure due to a terrorist attack, especially considering azide's online availability and ease of synthesis.

Treatment varied, depending on the scenario. Gastric lavage with or without activated charcoal may not be effective, because it is not known how long sodium azide, which is water soluble and generally ingested as a solution, would remain in the stomach, and it is unclear if azide actually binds to charcoal [79,80].

Since azide can cause profound hypotension, supportive care with vasopressors and large amounts of intravenous fluids is frequently needed. Two patients underwent hemodialysis, one of whom also received an intra-aortic balloon pump to maintain blood pressure [47,60]. The former treatment may be useful, because NaN_3 is a small molecule (65 kDa).

Although both azide and cyanide inhibit cytochrome C oxidase, it seems unlikely that sodium thiosulfate, amyl nitrite, or sodium nitrite would be useful against azide poisoning. Sodium thiosulfate detoxifies cyanide by converting it to thiocyanate; it seems unlikely that sodium thiosulfate would react with azide. Amyl nitrite and sodium nitrite generate methemoglobin, which scavenges cyanide, but methemoglobin binds azide only weakly (log $K_{observed} = 5.427$ at pH 7.02) [81]. Moreover, nitrites could be detrimental, because they generate nitric oxide, which could exacerbate azide-induced hypotension [82,83].

Hydroxocobalamin appears to be a reasonable treatment for azide poisoning, because cobalamin binds nitric oxide, and high doses of cobalamin raise blood pressure in control subjects, likely *via* reducing plasma nitric oxide concentrations [84,85]. Thus, cobalamin could potentially raise the blood pressure in azide-poisoned hypotensive patients.

Limitations

While two-thirds of the sources we included were peer-reviewed, all but one paper were case reports, which are prone to publication bias and therefore limited generalizability. The single case-control study relied on a work-medical history questionnaire, which is susceptible to recall bias.

As in other reviews of clinical cases, we were limited by whether someone chose to publish a case and whether a diagnosis was made appropriately. The former is exemplified in Hirose *et al.* where data on only seven of 10 azide-poisoned victims were provided [73]. The latter may be particularly problematic for azide poisoning, since it can be mistaken for cyanide poisoning due to mechanistic and symptomatic similarities. Taken together, the actual incidence of azide poisoning is likely to be greater than that reported. The cases reported in newspaper articles generally did not describe treatment strategies, limiting our ability to tie treatment to outcome.

Conclusions

Multiple routes of azide exposure exist, resulting in a variety of symptoms and range of disease severity. Treatment depends largely on the type, site, and degree of injury, and success can be ambiguous. Preventing or minimizing exposure, especially among high-risk persons, is the best strategy.

Laboratory workers should perform risk assessments to identify potential areas of concern prior to working with azide, and consideration should be given to limiting access to azide to prevent accidental or intentional ingestion. Concentrated azide solutions should not be exposed to shock or friction, or come into contact with heavy metals due to the possibility of explosion.

For medical personnel, the most likely exposure routes are inhalation of hydrazoic acid expired by (or lavaged from) a patient, dermal contact from sodium azide dust left on patients or their clothing, or eye exposure to hydrazoic acid or sodium azide dust. First responders should therefore wear safety goggles and gloves, and use CPR barrier devices where azide poisoning is possible. Moreover, any person suspected of azide poisoning should be decontaminated prior to hospitalization according to standard Hazmat protocols.

For severe systemic exposures to azide, hemodynamic support is clearly important, with some patients requiring aggressive therapy. Quantitative information on appropriate drugs is lacking, but, hydroxocobalamin is a rational choice based on its mechanism of action and relatively good safety profile.

Funding

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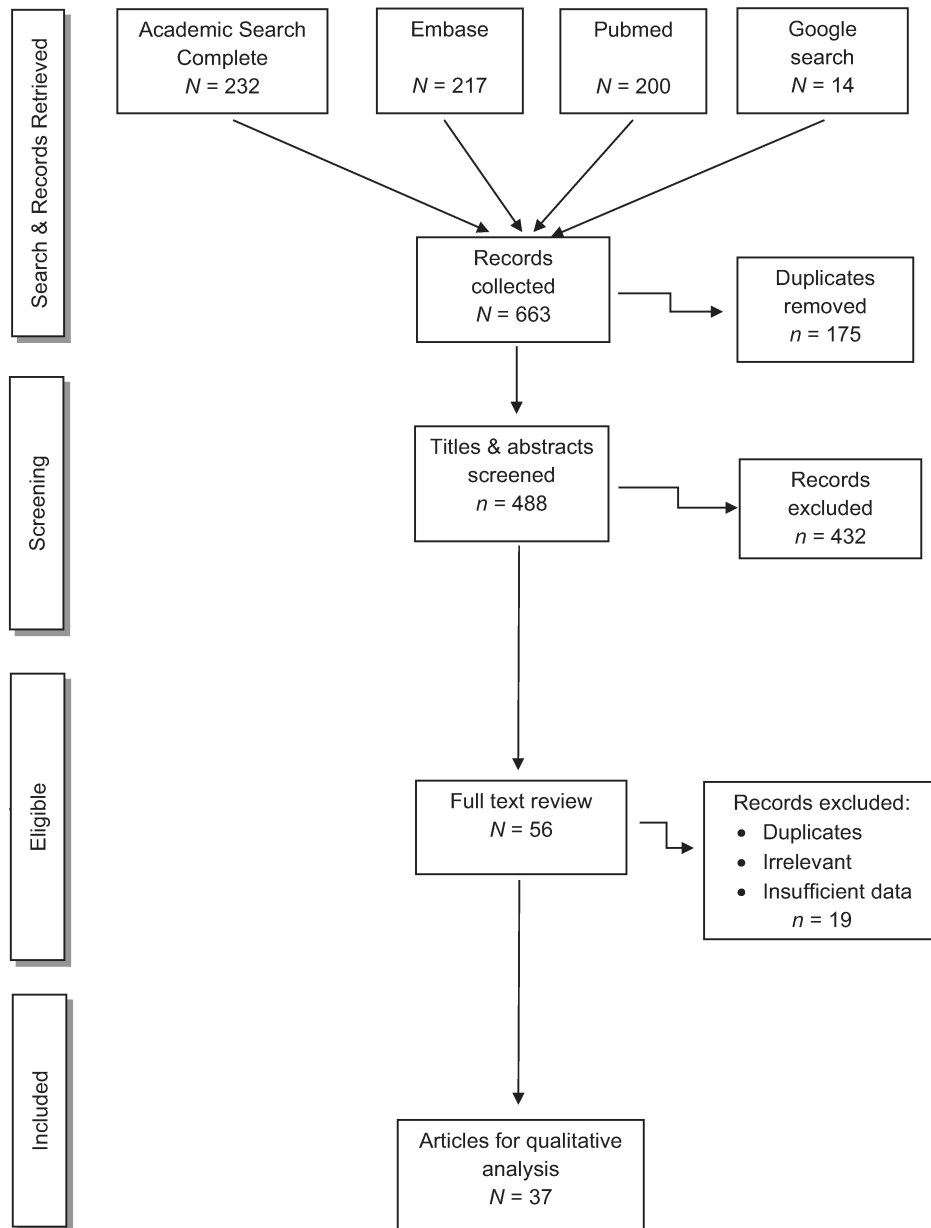
Figure 1.
Peer-reviewed articles concerning human cases of NaN_3 or HN_3 exposure.
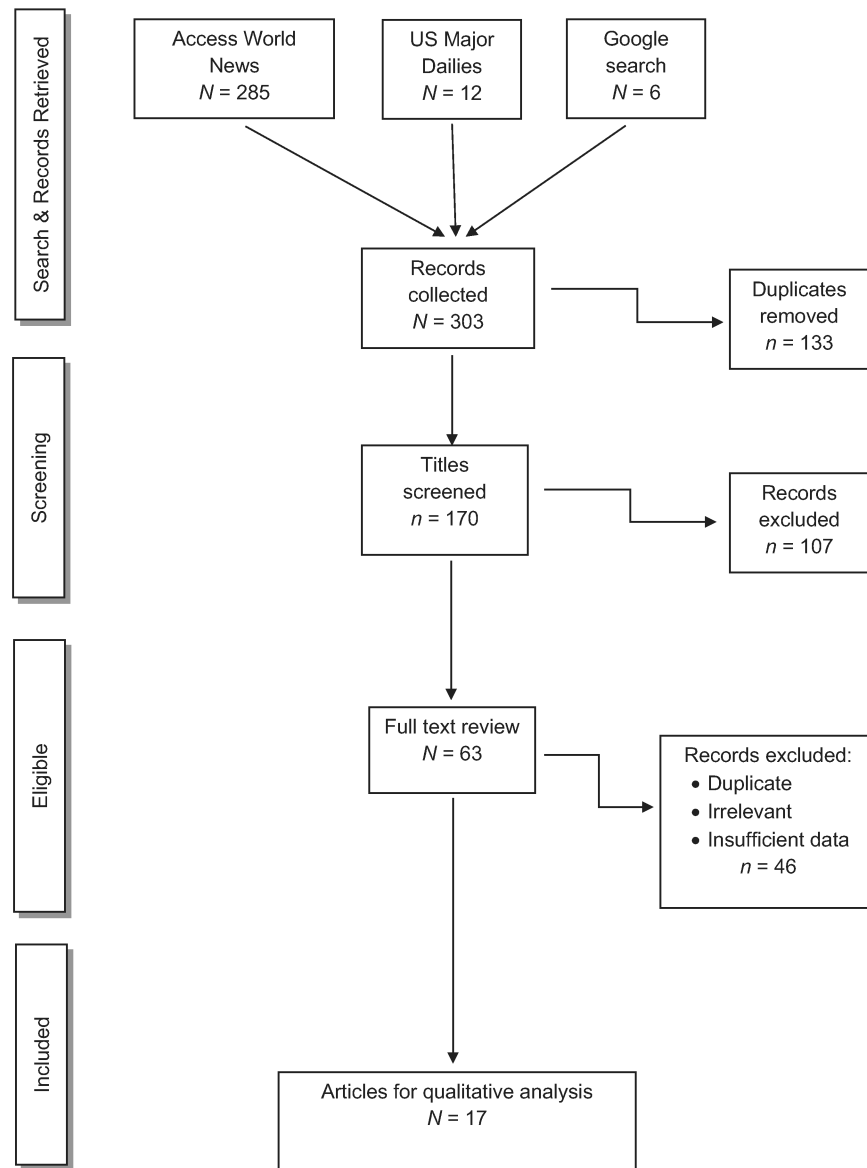
Figure 2.
News articles concerning human cases of NaN_3 or HN_3 exposure.

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Table 1.

Review of 37 peer-reviewed papers yielded 106 cases.

1A-1. Accidental exposure due to airbag deployment

Publication	Level of evidence	Number of cases	Gender	Age	Exposure route	Clinical features	Hospitalization	Treatment	Survival
Corazza et al. [24]	VII	1	Male	35	Dermal contact	First-degree burns Irritant contact dermatitis	Yes	Topical steroids	Yes
Foley and Helm [25]	VII	1	Female	32	Dermal contact	First-degree burns	Yes	Topical antibiotics	Yes
Corazza et al. [33]	VII	1	Male	36	Dermal contact	First and second-degree burns	Yes	Topical antibiotics	Yes
Wu et al. [26]	VII	1	Female	29	Dermal contact	Irritant contact dermatitis	Yes	Topical and oral steroids	Yes
Suhr and Kreusch [27]	VII	1	Female	73	Dermal contact	Second-degree burns	Yes	Topical antibiotics	Yes
Hambrook and Fink [28]	VII	1	Male	47	Inhalation	Asthma Chest tightness Cough	Yes	β-agonists Inhaled steroids	Yes
Caudle et al. [29]	VII	1	Male	18	Inhalation	Chemical pneumonitis Dyspnea Hemoptysis	Yes	Oral steroids Oxygen	Yes
Belhadj-Tahar et al. [32]	VII	1	Male	37	Inhalation and dermal contact	Burning eyes Dyspnea	Yes	Ocular irrigation Supplemental oxygen	Yes
Francis et al. [9]	VII	1	Male	22	Inhalation and dermal contact	Alkaline ocular injury Erythematous supraglottis Stridor Tachypnea	Yes	Mechanical ventilation Ocular irrigation Steroids	Yes
Govindarajan et al. [30]	VII	1	Male	56	Inhalation	Chemical pneumonitis	Yes	N/A	Yes
Sever et al. [31]	VII	3	Female Male	21 39 33	Dermal contact	All three had second-degree burns One patient had alkaline ocular injury	Yes	Standard burn care Victim with ocular burn received additional ophthalmic care	Yes

1A-2. Accidental exposure due to industrial work

Publication	Level of evidence	Number of cases	Gender	Age	Exposure route	Clinical features	Hospitalization	Treatment	Survival
Pham et al. [36]	VII	1	Male	29	Inhalation and dermal contact	Bradycardia Hypotension Metabolic acidosis Third-degree burns	Yes	Intravenous fluids Mechanical ventilation Sodium bicarbonate Vasopressors	No

Publication	Level of evidence	Number of cases	Gender	Age	Exposure route	Clinical features	Hospitalization	Treatment	Survival
Miljours and Braun [34]	IV	41	Unknown	Median age not available	Inhalation	Burning eyes Dizziness Headache Palpitations	No	Unknown	Yes
Fang et al. [35]	VII	1	Male	32	Inhalation and dermal contact	Diplopia Dizziness Paresthesias Reduced muscle strength	Yes	Hyperbaric oxygen Steroids Traditional Chinese medicines Vitamins B_1, B_{12}, and C	Yes

1A-3. Accidental exposure in a laboratory

Publication	Level of evidence	Number of cases	Gender	Age	Exposure route	Clinical features	Hospitalization	Treatment	Survival
Angelotti et al. [39]	VII	1	Male	33	Dermal contact (13 g)	Burns Hypotension Lacerations	Yes	Amputation Mechanical ventilation Vasopressors Wound care	Yes

1A-4. Accidental exposure in a medical facility

Publication	Level of evidence	Number of cases	Gender	Age	Exposure route	Clinical features	Hospitalization	Treatment	Survival
Watanabe et al. [47]	VII	1	Female	53	Ingestion (1 g)	Generalized seizures Hypotension Metabolic acidosis	Yes	Hemodialysis Gastric lavage with activated charcoal Intra-aortic balloon pump Intravenous steroids Mechanical ventilation Vasopressors	Yes
Dermican et al. [46]	VII	1	Female	25	Ingestion (0.1 g)	Generalized seizures Headache Vomiting	Yes	Gastric lavage	Yes

1B-1. Suicide in a laboratory setting

Publication	Level of evidence	Number of cases	Gender	Age	Exposure route	Clinical features	Hospitalization	Treatment	Survival
Spadafora et al. [40]	VII	1	Female	Unknown	Ingestion (>10 g)	Bradycardia Coma Hypoxia Metabolic acidosis	Yes	Unknown	No
Senda et al. [50]	VII	1	Female	25	Ingestion	Acute respiratory distress syndrome Arrythmia Cardiac arrest Coma Metabolic acidosis	Yes	Gastric lavage Intravenous steroids Mechanical ventilation Sodium bicarbonate	No

Publication	Level of evidence	Number of cases	Gender	Age	Exposure route	Clinical features	Hospitalization	Treatment	Survival
Fuyuno and Cyranoski [51]	VII	1	Male	42	Ingestion	N/A	No (found dead)	N/A	No
Łopaciński et al. [52]	VII	2	Male	30	Ingestion (>0.18g)	Dizziness Metabolic acidosis Tachycardia	Yes	Inhaled amyl nitrite Intravenous sodium nitrite Intravenous sodium	Yes
				23	Ingestion (10 g)	Arrythmia Cardiac arrest Coma Metabolic acidosis	Yes	thiosulfate	No
Meatherall and Palatnick [53]	VII	1	Male	59	Ingestion	Arrythmia Cardiogenic shock Coma Hypotension Metabolic acidosis	Yes	Exchange transfusion Inhaled amyl nitrite Intravenous sodium nitrite Intravenous sodium thiosulfate Mechanical ventilation Sodium bicarbonate Vasopressors	No
French et al. [54]	VII	1	Male	28	Ingestion (0.1 g)	Bradycardia Hypotension Metabolic acidosis	Yes	Intravenous fluids Gastric lavage Sodium bicarbonate	Yes
Kostek et al. [55]	VII	1	Female	55	Ingestion (0.6 g)	Metabolic acidosis	Yes	Gastric lavage	Yes
Le Blanc-Louvry et al. [56]	VII	1	Male	35	Ingestion (6g)	N/A	No (found dead)	N/A	No
Bartecka-Mino et al. [57]	VII	1	Female	25	Ingestion	Coma Hypotension Metabolic acidosis	Yes	Hydroxocobalamin Vasopressors	Yes
Downes et al. [58][a]	VII	1	Male	32	Ingestion	Hypotension Metabolic acidosis	Yes	Intravenous fluids Vasopressors	No
Gao et al. [60][b]	VII	1	Male	23	Ingestion (1.38 g)	Chest pain Hypotension Metabolic acidosis Nausea and vomiting	Yes	Hemodialysis Intravenous crystalloid Norepinephrine	Yes
Muvalia et al. [59]	VII	1	Female	19	Ingestion (50 g)	Coma Hypotension Metabolic acidosis Nausea and vomiting	Yes	Mechanical ventilation Vasopressors	No

1B-2. Suicide in a non-laboratory setting

Publication	Level of evidence	Number of cases	Gender	Age	Exposure route	Clinical features	Hospitalization	Treatment	Survival
Wiergowski et al. [61]	VII	1	Male	19	Ingestion (~20 g)	N/A	No (found dead)	N/A	No
Meatherall and Oleschuk [53]	VII	1	Male	35	Ingestion	N/A	No (found dead)	N/A	No
Overtchouk et al. [63]	VII	1	Female	69	Ingestion (15g)	Myocardial dysfunction Metabolic acidosis	Yes	Gastric lavage Intravenous fluids	Yes

Publication	Level of evidence	Number of cases	Gender	Age	Exposure route	Clinical features	Hospitalization	Treatment	Survival
Rojek et al. [64]	VII	1	Female	50	Ingestion	Bradycardia Coma Hypotension	Yes	Mechanical ventilation Vasopressors	No
Ciesla et al. [65]	VII	1	Male	24	Ingestion	Coma	Yes	Unknown	No
Leonard et al. [2]	VII	1	Male	22	Ingestion (40 g)	Arrhythmia Cardiac arrest Hypotension Metabolic acidosis	Yes	Mechanical ventilation	No

1C. Secondary exposure of emergency medical personnel

Publication	Level of evidence	Number of cases	Gender	Age	Exposure route	Clinical features	Hospitalization	Treatment	Survival
Hirose et al. [73]c	VII	6	Unknown	Unknown	Inhalation	Burning eyes Dizziness Dyspnea Headache	No	Unknown	Yes
Downes et al. [58]a	VII	10	5 Males 5 Females	39 (median)	Inhalation and dermal contact	1 case reported fatigue 1 case reported stress	No	Time off from work for the two cases	Yes

1D. Unknown exposure

Publication	Level of evidence	Number of cases	Gender	Age	Exposure route	Clinical features	Hospitalization	Treatment	Survival
Hirose et al. [73]c	VII	7	1 Female 6 Males	22 20 24 24 43 55	Ingestion	Dizziness Hypotension Palpitations Paresthesias Syncope	Yes	Gastric lavage Inhaled amyl nitrite Intravenous sodium nitrite Intravenous sodium thiosulfate Vasopressors	Yes
Schwarz et al. [74]	VII	5	3 Females 2 Males	Median age not available	Ingestion	Arrhythmia Headache Hypotension	Yes	Intravenous fluids Oral antiemetics	Yes

They are grouped based on mode of azide exposure (i.e., accidental, suicidal, secondary, and unknown, letters A through D, respectively) and sub-grouped based on exposure setting (numbers 1 through 4). Unless indicated, an entry is a primary patient.

a Downes et al. [58] reported a total of 11 patients. The primary victim committed suicide by azide ingestion and is described in Table 1(B-1). Ten medical personnel who treated the patient are described in Table 1(C).

b Although not in the abstract, we contacted the corresponding author who confirmed the patient ingested azide to commit suicide.

c Ten patients were exposed to azide and hospitalized. Hirose worked at the hospital where seven of the patients were treated. Hence, the paper provided data on only those seven victims; they are summarized in Table 1(D) (information was not provided on whether poisoning was intentional or accidental). Six medical personnel who treated the seven azide-poisoned patients presented symptoms consistent with low-dose azide exposure, likely *via* inhaling HN3 gas released when performing gastric lavage on the patients. They are described in Table 1(C).

Table 2.

Review of 17 news articles yielded 50 cases.

2A-1. Accidental exposure due to industrial work

Publication	Number of cases	Gender	Age	Exposure route	Clinical features	Hospitalization	Survival
Perkins [37]	1	Male	45	Dermal contact	Burned >15% of body	Yes	No

2A-2. Accidental exposure in a laboratory

Publication	Number of cases	Gender	Age	Exposure route	Clinical features	Hospitalization	Survival
Green [41]	1	Male	Unknown	Dermal Contact (65 g)	Burns	Yes	Yes
Author unknown [44]	1	Male	Unknown	Ingestion	Unknown	Yes	Yes
Lillington [40]	11	Unknown	Unknown	Inhalation	Unknown	Yes	Yes
Crabbe [42][a]	1	Male	27	Dermal contact	Facial burns Glass embedded in chest and abdomen Minor lacerations	Yes	Yes
Kemsley [43]	1	Male	Unknown	Dermal contact (200 g)	Second-degree burns Minor lacerations	Yes	Yes
Author unknown [45]	1	Male	Unknown	Dermal contact	Minor lacerations	Yes	Yes

2A-3. Accidental exposure in a medical facility

Publication	Number of cases	Gender	Age	Exposure route	Clinical features	Hospitalization	Survival
Author unknown [48]	1	Male	66	Ingestion (1 –5 g)	Rapid deterioration Vomiting	Yes	No

2B. Suicide in a non-laboratory setting

Publication	Number of cases	Gender	Age	Exposure route	Clinical features	Hospitalization	Survival
DeMare [67][b]	1	Female	32	Ingestion	Unknown	No (found dead)	No
Stout [68][c]	1	Female	25	Ingestion	Unknown	Yes	No
Bender [66]	1	Female	71	Ingestion	N/A	No (found dead)	No
Singh [69]	1	Male	21	Ingestion	Unknown	Yes	No
Hicks [70][d]	1	Male	27	Unknown	N/A	No (found dead)	No

2C. Homicide

Publication	Number of cases	Gender	Age	Exposure route	Clinical features	Hospitalization	Survival
Author unknown [48]	3	Unknown	Unknown	Ingestion (20 g)	Unknown	1 Yes 2 No	Yes
State of Arizona, Appellee, v. Wendi Elizabeth Adriano, Appellant [72]	1	Male	33	Ingestion (possibly 21 g)	N/A	No (found dead)	No

2D. Secondary occupational exposure of medical personnel

Publication	Number of cases	Gender	Age	Exposure route	Clinical features	Hospitalization	Survival
DeMare [67][b]	5	Unknown	Unknown	Unknown	Minor respiratory symptoms	Yes	Yes
Crabbe [42][a]	1	Male	25	Dermal contact	Facial and corneal burns	Yes	Yes
Stout [68][c]	6	Unknown	Unknown	Unknown	Unknown	Yes	Yes
Hicks [70][d]	1	Unknown	Unknown	Unknown	Unknown	Yes	Yes

2E. Unknown exposure

Publication	Number of cases	Gender	Age	Exposure route	Clinical features	Hospitalization	Survival
Author unknown [75]	6	1 Male 1 Female 4 Unknown	Unknown	Ingestion	Dizziness Syncope Tinnitus	Yes	Yes
Author unknown [76]	4	Unknown	Unknown	Ingestion	Dizziness Lightheadedness	Yes	Yes

They are grouped based on mode of azide exposure (i.e., accidental, suicidal, homicidal, secondary, and unknown, letters A through E, respectively) and sub-grouped based on exposure setting (numbers 1 through 3). Unless indicated, an entry is a primary patient.

[a]Crabbe [42] reported two patients. The primary victim was exposed to azide in a laboratory explosion and is described Table 2(A-2). A firefighter was exposed to azide while responding to the primary victim and is described in Table 2(D).

[b]DeMare [67] reported six patients. The primary victim committed suicide by ingesting azide and is described Table 2(B). Five emergency response personnel who came into contact with the primary victim are described in Table 2(D).

[c]Stout [68] reported seven patients. The primary victim committed suicide by ingesting azide and is described Table 2(B). Six emergency response personnel who came into contact with the primary victim are described in Table 2(D).

[d]Hicks [70] reported two patients. The primary victim committed suicide with azide *via* an unknown route and is described Table 2(D). Among personnel who responded to the victim, one officer was hospitalized for observation and is described in Table 2(D).