Human Health Effects of Sodium Azide Exposure: A Literature Review and Analysis

Soju Chang[1] and Steven H. Lamm[1,2]

[1]*Preventive Medicine Residency Program, John Hopkins Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Maryland, USA*
[2]*Consultants in Epidemiology and Occupational Health, Inc., Washington DC, USA*

Sodium azide, used mainly as a preservative in aqueous laboratory reagents and biologic fluids and as a fuel in automobile airbag gas generants, has caused deaths for decades. Its exposure potential for the general population increases as the use of airbags increase. In order to characterize the known health effects of sodium azide in humans and the circumstances of their exposure, the authors conducted a systematic review of the literature from 1927 to 2002 on human exposure to sodium azide and its health effects. The most commonly reported health effect from azide exposure is hypotension, almost independent of route of exposure. Most industrial exposures are by inhalation. Most laboratory exposures or suicide attempts are by ingestion. Most of the reported cases involved persons working in laboratories. The time between exposure and detection of hypotension can predict outcome. Fatal doses occur with exposures of $\geq$700 mg (10 mg/kg). Nonlethal doses ranged from 0.3 to 150 mg (0.004 to 2 mg/kg). Onset of hypotension within minutes or in less than an hour is indicative of a pharmacological response and a benign course. Hypotension with late onset ($>$1 hour) constitutes an ominous sign for death. All individuals with hypotension for more than an hour died. Additional health effects included mild complaints of nausea, vomiting, diarrhea, headache, dizziness, temporary loss of vision, palpitation, dyspnea, or temporary loss of consciousness or mental status decrease. More severe symptoms and signs included marked decreased mental status, seizure, coma, arrhythmia, tachypnea, pulmonary edema, metabolic acidosis, and cardiorespiratory arrest. The signs and symptoms from lower exposures ($<$700 mg) are physiological responses at the vascular level and those at or above are toxicological responses at the metabolic level. There is no specific antidote for sodium azide intoxication. Recommended preventive measures for sodium azide exposure consist of education of people at high risk, such as laboratory workers, regarding its chemical properties and toxicity, better labeling of products containing sodium azide, and strict enforcement of laboratory regulations and access control.

Keywords Airbags, Human Health, Hypotension, Laboratory Regulation, Literature Review, Sodium Azide

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Address correspondence to Steven H. Lamm, MD, DTPH, Consultants in Epidemiology and Occupational Health, Inc., 2428 Wisconsin Avenue, NW, Washington, DC 20007, USA. E-mail: steve@ceoh.com

Sodium azide (NaN_3) is a white to colorless, crystalline powder that is highly water soluble, tasteless, and odorless. In the United States, estimated demand peaked at 10 to 12 millions pounds driven by its use in automotive airbags (Fattah 1996); however, this is already in decline as sodium azide–based airbags are being phased out in favor of less toxic materials. As an airbag constituent, sodium azide produces sodium oxide and nitrogen gas. The sodium oxide will react with water to form sodium hydroxide. Use of sodium azide in the automobile airbags has increased the potential for direct human exposure through operations such as transportation, manufacturing, assembly, repair, dismantling, and scraping. Handling azide and azide-containing mixtures is of some concern due to both toxicity and combustibility issues. However, according to J. M. Hitt, azide toxicity should not be a problem in these circumstances (Hitt 1992).

Increased production and disposal of azides have increased the potential for human exposure and for contamination of environment. Azides are highly water-soluble and are stable in neutral to caustic solution in the absence of light, but will photolytically decompose via sunlight. Photolysis of sodium azide may result in metal nitrides initially, with the eventual formation of the free metal and nitrogen gas (United States Environmental Protection Agency [US EPA] 1977).

NaN_3 is the conjugate base of hydrazoic acid, $HN_{3(aq)}$, a weak acid. When in contact with moisture, NaN_3 can be released to water wherein an equilibrium amount of $HN_{3(aq)}$ forms ($NaN_3 + H_2O \leftrightarrow HN_{3(aq)} + N^-_{3(aq)} + Na^+ + OH^-$). In turn, $HN_{3(aq)}$ participates in equilibrium with the vapor phase in the form of hydrogen azide gas, $HN_{3(gas)}$. As pH of the moist material becomes increasingly acidic, the mole fraction of $HN_{3(aq)}$ increases and thereby the vapor pressure of $HN_{3(gas)}$.

Betterton et al. (1997, 1999) have asserted that the ultimate environmental fate of sodium azide, including the breakdown products of sodium azide in soil, is unknown. However, there is good information available, particularly from the days in which sodium azide was used for soil application as a herbicide and a soil fumigant. Sodium azide was applied at a level of 40 to

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120 lbs/acre as a nonselective broad-spectrum herbicide against both annual and perennial weeds (Ahrens 1983).

The 1983 *Herbicide Handbook*, 5th Edition, notes that sodium azide is not absorbed to any great degree by mineral soils but is absorbed by muck soils. It may be converted to hydrazoic acid in acid soils, and both it and hydrazoic acid are readily leachable. Because of azide's easy leachability, photodecomposition is not an important means of dissipation. Azide dissipates quite rapidly in soils by oxidation or by reaction of hydrazoic acid with organic acids to form azides of these acids, which then decompose by the Curtius arrangement ($RCON_3 \rightarrow RNCO + N_2$). Reaction of the isocyanate (RNCO) with water causes the additional release of carbon dioxide ($2\ RNCO + H_2O \rightarrow RNHCONHR + CO_2$). Higher temperatures and lower soil pH levels accelerate dissipation. Opinions differ as to whether the oxidation of azide is microbially produced by soil bacteria and fungi or strictly by a chemical process accelerated by increasing acidity and elevated temperature (Hitt 1992; Ahrens 1983). The *Herbicide Handbook* took its reference for this section from Bradbury et al. (*Ann. Applied. Biol.* 45:241–250). Because sodium azide has been widely used as a bactericide, it is unlikely that naturally occurring bacteria are likely to break it down. However, with the development of widespread bioremediation for other chemicals, it is difficult to rule out the possibility of bioengineering a bug capable of azide decomposition.

Sodium azide, when heated in air to 275°C to 330°C, decomposes to nitrogen and leaves a residue of sodium oxide (American Conference of Governmental Industrial Hygienists [ACGIH] 1991). This chemical reaction is the basis of its use in airbags. In airbags, the azide pellet is composed of azide mixed with an oxidizing agent and with burn rate modifiers that produce a given controlled burn rate. This results in an airbag inflated with nitrogen gas and a white powder residue of sodium oxide.

Two routes to manufacturing sodium azide have been commercialized. Newer plant capacity in Japan and India derive sodium azide from hydrazine. Historical sources in Canada, United States, and Germany derive sodium azide from reaction of elemental sodium with ammonia to form sodium amide that in turn reacts with nitrous oxide (Rippen et al. 1996).

Sodium azide has many applications in commerce. In addition to use in automobile airbags, it has also has been evaluated for use as a herbicide, insecticide, nematocide, fungicide, and a bactericide (ACGIH 1991; Trochimowicz 1990). It has been widely used in clinical laboratories as a preservative in reagents such as diluting fluids for counting red blood cells (0.1%), and buffering solutions used to screen for hepatitis antigen (4.0%). Other industrial usages include the manufacturing processes of rubber, latex, wine, seed, Japanese beer, and an intermediate in the production of lead azide.

According to data collected during the early 1980s, the National Institute for Occupational Safety and Health (NIOSH) considers nearly 55,000 workers in the United States exposed to sodium azide. The primary human health effect of concern is the hypotensive effect of sodium azide. These data do not include potential occupational exposures to sodium azide in the airbag industry, exposures that might occur with sodium azide production, airbag manufacturing, installation, and recycling (Trout et al. 1996).

Absorption of particulate, liquid solution, or vapor phases of sodium azide can involve ingestion, inhalation, or cutaneous routes of exposure. The ACGIH established a threshold limit value (TLV) for sodium azide in 1976 and revised it in 1992. ACGIH reviewed evidence of skin absorption to add to the TLV in 1992 (ACGIH 1991). As of 1992, the Occupational and Safety Health Administration (OSHA) and the NIOSH added skin notations to their vacated permissible exposure limit (PEL) and recommended exposure limit (REL), respectively (OSHA 1989).

Sodium azide absorbs quickly from the gastrointestinal tract, from injection sites, and from the respiratory tract (Bassendowska 1962; Reinhardt and Brittelli 1981). The degree to which sodium azide permeates the skin is unclear. It is metabolized in the liver, and excreted by the kidneys (Trochimowicz 1990). Detailed data about human absorption, metabolism, distribution, and elimination are not available.

Both sodium azide and hydrazoic acid vapor cause similar health effects in animals and in humans. The hypotensive response to sodium azide relates to peripheral blood vessel dilatation, but no one knows the proximal cause of dilation. Primary reviews by Klein-Schwartz and coworkers, Smith and coworkers, and Chiba and coworkers described sodium azide intoxication cases, which established the hypotensive effect (Klein-Schwartz et al. 1989; Smith and Wilcox 1994; Chiba, Ohmichi, and Inaba 1999). Each article described a different part of the literature and added new cases. Azide or hydrazoic acid or even nitric oxide (NO), formed by biotransformation of azide, might be responsible. Azides also might affect carotid body chemoreceptors, cardiac muscle, or coronary blood vessels (Graham 1949; Kleinhofs, Owais, and Nilan 1978).

In the late 1940s, Maurice Black of New York University examined various known inhibitors of carbohydrate metabolism (e.g., sodium azide, sodium fluoride, indoacetic acid, and malonic acid) to learn whether they might be effective in the treatment of acute leukemia and other diverse malignancies. He observed that sodium azide caused a temporary lowering of blood pressure toward normotensive levels in cancer patients with coexistent hypertension (Black 1947).

Black et al. explored this incidental finding, using sodium azide both acutely and chronically to observe its hypotensive action in both hypertensive and normotensive patients. They investigated 35 experimental subjects (26 hypertensive and 9 normotensive) for acute effects and 39 patients (30 hypertensive and 9 normotensive) for chronic effects, with oral daily doses ranging from 0.3 to 3.9 mg/day for up to 2 years. During the acute exposure studies, only one patient complained about a transient pounding sensation in the head shortly after taking the drug. They observed induced sensitivity in 20 hypertensive patients with continued use of sodium azide, requiring reduction

of daily doses from 0.5 to 0.25 mg three times a day. They did not observe hypotensive sensitization to sodium azide in normotensive patients. For three patients taking daily doses for more than 1 year, no evidence of kidney, heart, or liver damage based on routine clinical studies were found (Black 1954).

The exact mechanism of the toxicity of sodium azide remains unknown. In 1955, Robertson and Boyer postulated that the inhibition of heme-type enzymes, such as catalase, peroxidase, and cytochrome oxidase, was metabolically responsible for its toxicity (Robertson and Boyer 1954; Trochimowicz 1990). Later, Smith et al. showed that it was unlikely that this metabolic mechanism accounted for its lethality (Smith et al. 1991). Subsequently, Smith et al. showed that enhanced excitatory transmission in the central nervous system after conversion of sodium azide to nitric oxide was a more likely explanation for its lethality (Smith and Wilcox 1994). They explained lethality as a neurotransmitter effect rather than a metabolic effect. In the cardiovascular system, stimulation of carotid body chemoreceptors, stimulation of cardiac muscle, or dilation of coronary vessels may account for the hypotensive effect of sodium azide. Sodium azide produces tachycardia (rapid heart beat) centrally rather than by carotid sinus reflex response to falling blood pressure (Trochimowicz 1990; Smith and Wilcox 1994; Smith et al. 1991).

PURPOSE

This report characterizes the known health effects of sodium azide in humans and the circumstances of their exposure through a systematic review of the scientific literature.

Methods

Besides citations in major toxicological references and textbooks, we searched the National Library of Medicine's MEDLINE database and Hazardous Substances Databank (HSDB) through October 1, 2002 (ACGIH 1991; Trochimowicz 1990; Gosselin et al. 1984; Leikin and Paloucek 1998). These publications led to additional primary citations. The search included all languages. We obtained translations of relevant non-English language articles. We reviewed the publications and initially grouped them into two categories: case reports and human studies. In particular, we expanded on three reviews of human experience with sodium azide (Klein-Schwartz et al. 1989; Smith and Wilcox 1994; Chiba et al. 1999). Each review describes a different, sometimes overlapping, portion of the literature with the addition of new cases. In this paper, we integrate all data from these reviews with an updated collection of other publications about the health effects of sodium azide in humans.

We systematically abstracted demographic, occupational, medical, and toxicological data from these papers. We extracted data, if any, on the following variables into a Microsoft Access Database: age, gender, chemical, circumstance, occupation, route, dose, health effect, clinical outcome, therapeutic modality, and pathological findings at autopsy. A race variable was not included due to lack of information on this variable in most of the publications.

For our analysis, we defined a case as a single individual reported in the publications to have symptoms attributed to sodium azide exposure. We further categorized the age variable into children (<18 years old) and adult: young (18 to 35 years old, middle aged (36 to 65 years old), and elderly (>65 years old). We subcategorized the chemical exposure variable to sodium azide or to its by-products and hydrazoic acid. We divided the circumstances of exposure into occupational (including work accidents and occupational studies) and nonoccupational exposures (including accidental poisoning, suicides and experimental studies). We summarized the routes of exposure as oral, inhalation, parenteral, or direct contact (eye or skin). We defined health effects here as any symptom or sign reported in the publication, and clinical outcome was the disposition of the individual categorized as dead or alive. Exposures were reported in, or converted to, mg/kg, using 70-kg as the standard weight independent of gender and age. When a range of doses was reported, the lowest dose was chosen for the calculation.

We divided the analysis of the data into two parts. The first part was a descriptive analysis of the demographic information and case distribution by circumstances, routes, and clinical outcomes of exposure. In addition, the fatality rate was calculated using the number of deaths as the numerator and the total number of cases as the denominator by each category of the circumstance.

The second part of the analysis focused on the health effects of sodium azide in humans. We took two approaches to describe the toxicological data of sodium azide: one was case-based and stratified by routes of exposure, in which the health effects were grouped into categories by organ systems and quantified by the number of cases who presented such health effects. We also reported the onset of these health effects in this part. The other approach was non–case-based, in which each of the reported health effects was plotted into a diagram with range of exposures in the vertical axis and the categories of health effects by organ systems in the horizontal axis. We derived the dose-health effect diagram from case reports in which the exposure dosage information was stated or capable of estimation.

RESULTS

Thirty-eight (38) publications, dating from 1927 to 1999, either as full articles, abstracts, or letters to the editor, comprised all of the published literature about human health effects of sodium azide. Of the publications, 32 were case reports, 5 were occupational studies, and 1 was an experimental study.

We identified a total of 185 individual cases among the 38 publications (Table 1), of which 116 cases were obtained from human studies and 69 cases from case reports. We obtained information about one case from two independent reports of that case (Judge and Ward 1989; Howard et al. 1990). Two publications of human studies did not have information on the number of cases (Haas and Marsh 1970; Rippen et al. 1996). The 185 cases

TABLE 1
Circumstances of sodium azide and hydrazoic acid exposure and clinical outcomes

Route	Chemical	Exposure dosage	Circumstance	Case	Outcome	Reference	Year[a]
I. Case reports ($n = 69$)							
Oral ($n = 43$)	Sodium azide	N/A[b]	Work accident[c]	2	Dead	Singh	1994
		N/A[b]	Suicide[c]	1	Dead	Lambert	1995
		N/A[b]	Suicide	1	Dead	Klein-Schwartz	1989
		N/A[b]	Suicide	1	Dead	Chiba	1998
		N/A[b]	Suicide[c]	1	Dead	Wollenck	1989
		N/A[b]	Suicide	1	Dead	Emmet	1975
		Several grams	Suicide	1	Dead	Kozlicka-Gajdzinska	1966
		55 g	Suicide	1	Dead	Klein-Schwartz	1989
		15 to 20 g	Suicide[c]	1	Dead	Abrams	1987
		10 to 20 g	Suicide[c]	1	Dead	Albertson	1986
		15 g	Suicide[c]	1	Dead	Klug	1987
		9 g	Suicide[c]	1	Dead	Marquet	1996
		$\geq$8.8 g	Suicide[c]	1	Dead	Peclet et Ponton	1991
		1.2 to 2 g	Suicide[c]	1	Dead	Klein-Schwartz	1989
		1 g	Poisoning[c]	1	Dead	Herbold	1995
		700 to 800 mg	Poisoning[c]	1	Dead	Judge	1989
		150 mg	Work accident[c]	1	Alive	Burger	1965
		90 mg	Poisoning	1	Alive	Tsujikawa	1998
		50 to 60 mg	Poisoning[c]	1	Alive	Richardson	1975
		20 to 80 mg	Work accident[c]	5	Alive	Edmonds	1982
		5 to 10 mg	Poisoning	1	Alive	Kayser	1928
		5 to 10 mg	Work accident[c]	1	Alive	Richardson	1975
		4 mg	Work accident[c]	1	Alive	Roberts	1974
		3 to 5 mg (3 sips)	Poisoning[c]	1	Alive	Howard	1990
		N/A[b]	Poisoning[c]	1	Alive	Roberts	1974
		N/A[b]	Work accident	8	Alive	Chiba	1998
		N/A[b]	Poisoning	2	Alive	Tsujikawa	1998
		N/A[b]	Work accident	3	Alive	Tsujikawa	1998
Inhalation ($n = 12$)	Hydrazoic acid (vapor)/sodium azide (particulate)	N/A[b]	Work accident[c]	1	Alive	Stern	1927
		N/A[b]	Work accident[c]	1	Alive	Reinhardt	1981
		N/A[b]	Work accident	3	Alive	Tsujikawa	1998
		N/A[b]	Work accident[c]	1	Alive	Rentsch	1956
		N/A[b]	Work accident[c]	2	Alive	Weiss	1996
		N/A[b]	Work accident[e]	3	Alive	Gobbi	1967
		3 deep breaths	Exp[g] self study[c]	1	Alive	Kocher	1930
Intravenous ($n = 9$)	Sodium azide	N/A[b]	Poisoning (dialysis center)	9	Alive	Gordon	1990
Direct contact ($n = 5$)	Sodium hydroxide[f]/ sodium azide	N/A[b]	Car accident	1	Alive	Ingraham	1991
		N/A[b]	Car accident	1	Alive	Smally	1992
		N/A[b]	Car accident	1	Alive	White	1995
		N/A[b]	Work accident	1	Alive	Tsujikawa	1998
		N/A[b]	Work accident (warehouse)	1	Dead	Gesell	1997

(Continued on next page)

TABLE 1
Circumstances of sodium azide and hydrazoic acid exposure and clinical outcomes *(Continued)*

Route	Chemical	Exposure dosage	Circumstance	Case	Outcome	Reference	Year[a]
II. Human studies ($n = 116$)							
Oral ($n = 73$)	Sodium azide	0.65 mg	Exp[g] therapeutic study	16	Alive	Black	1954
		1.3 mg	Exp[g] therapeutic study	19	Alive	Black	1954
		0.3 to 3.9 mg	Exp[g] therapeutic study	38	Alive	Black	1954
Inhalation ($n = 42$)	Hydrazoic acid (vapor)/sodium azide (particulate)	0.5 to 65 ppm	Exp[g] Occ[h] study[c]	N/A[b]	Alive	Haas	1970
		ND[i] to 0.6 ppm	Exp[g] Occ[h] study[e]	11	Alive	Trout	1996
		0.3 to 3.9 ppm	Exp[g] Occ[h] study[e, f]	10	Alive	Graham	1948
		N/A[b]	Exp[g] Occ[h] study[e]	N/A[b]	Alive	Rippen	1996
		N/A[b]	Exp[g] Occ[h] study[e]	21	Alive	Lamm	1999
Intravenous ($n = 1$)	Sodium azide	1.3 mg	Exp[g] therapeutic study	1	Alive	Black	1954

[a]Year of publication. [b]No information available. [c]Laboratory. [d]Transportation. [e]Azide industry. [f]Lead azide industry. [g]Experimental. [h]Occupational. [i]Not detectable.

included 2 children (1%) and 183 adults (99%) with the following age distribution: young individuals accounted for 11% of cases, middle-aged individuals for 10%, adult age not other specified for 74% of cases, and elderly for 4%. For those 47 cases with age specified, the median age was 38 years old with a range of 2 to 75 years old. The gender distribution was 37 males, 22 females, and 126 with gender unspecified.

We classified the 185 cases (Table 1) by route of exposure, outcome (dead/alive), and dose (amount of exposure). In summary, 116 cases were exposed by the oral route, 54 cases by inhalation, 10 cases by the parenteral route (intravenous), and 5 cases by the direct contact route (skin and eye). Deaths occurred among the oral-exposed group, except one case with dermal exposure. This individual suffered a 45% of body burn from a metal azide explosion and presumably absorbed azide dermally or by subdermal tissue absorption in the burn areas. Of the 18 publications with quantitative information for the oral route, exposure ranged from 0.3 mg to 55 g. The 9 cases who died after known or estimated oral exposures ingested 700 mg or more, whereas the remaining cases that recovered had ingestion exposures ranging from 0.3 mg to 150 mg. The estimated smallest lethal dose was 10 mg/kg. In that particular case, however, the body weight was given as 52 kg and the dose would be 13.4 mg/kg (Judge and Ward 1989). The 17 ingestion deaths occurred after suicides (13), laboratory work accidents (2), and laboratory poisonings (2), and 1 direct exposure death occurred after a work accident in a warehouse. Eight of the 13 suicide deaths and both of the poisoning and work accident deaths were laboratory related (Table 1).

Table 2 presents an analysis of the circumstances of the cases. Occupational exposures accounted for 41.6% (77/185) of the reported sodium azide cases, whereas nonoccupational exposures accounted for 58.4% (108/185). The occupational exposure cases where the occupational site was described included work accidents in the laboratory (13 cases), in the azide manufacturing industry (3 cases), in a cargo transport area of an airport (2 cases), and in a warehouse (1 case). The occupational site was not described for 15 cases. The laboratory accident cases involved both ingestion and inhalation exposures. The azide industry and cargo transport accidents involved only inhalation. The work accident in the warehouse was through dermal exposure with burns over almost half the body area. The occupational studies reported 42 cases among an unknown number of exposed workers. The nonoccupational exposure cases ($n = 108$ cases) consisted of 74 individuals involved in an experimental therapeutic study, 18 poisonings, 13 suicides, and 3 traffic accidents. Overall, the most common route of exposure was oral (62.7%), followed by inhalation (29.2%), intravenous (5.4%), and direct contact (2.7%).

The overall death rate among reported cases (case fatality rate) was 9.7%, with most of the deaths among those with oral exposure (case fatality rate = 14.7%). Laboratory workers with accidental oral exposure had a case fatality rate of 20%. Nonoccupational deaths only occurred among suicides and poisonings with oral exposure (case fatality rates = 100% and 22.2%, respectively).

The time from death to the discovery of the cases (not shown) varied from 30 minutes to 84 hours, with a median interval of 4 hours and 20 minutes. Of those who survived, the oral-exposure group had recovery times from 2 hours to 10 days and the inhalation-exposed group had intervals that ranged from several days to nearly a month.

Table 3 describes human health effects categorized by organ systems and by comparative frequency of cases presenting such health effects by route of exposure. Hypotension was the most commonly reported health effect ($n = 120$). Direct contact

TABLE 2
Distribution of individual cases by route, circumstance, and clinical outcome of exposure

	Outcome	Oral	Inhalation	Intravenous	Direct	Total
I. Case Reports: $n = 69$ (37.3%)						
Occupational						
Work accident						
1. Laboratory: $n = 13$ (18.8%)	Alive	8	3	0	0	11
	Dead	2	0	0	0	2
	Total	10	3	0	0	13
	Fatality rate	20.0%	0.0%	—	—	15.4%
2. Azide industry: $n = 3$ (4.3%)	Alive	0	3	0	0	3
	Dead	0	0	0	0	0
	Total	0	3	0	0	3
	Fatality rate	—	0.0%	—	—	0.0%
3. Transportation/warehouse: $n = 3$ (4.3%)	Alive	0	2	0	0	2
	Dead	0	0	0	1[c]	1
	Total	0	2	0	1	3
	Fatality rate	—	0.0%	—	100.0%	33.3%
4. No information: $n = 15$ (21.7%)	Alive	11	3	0	1[a]	15
	Dead	0	0	0	0	0
	Total	11	3	0	1	15
	Fatality rate	0.0%	0.0%	—	0.0%	0.0%
Self experiment						
Laboratory: $n = 1$ (1.4%)	Alive	0	1	0	0	1
	Dead	0	0	0	0	0
	Total	0	1	0	0	1
	Fatality rate	—	0.0%	—	—	0.0%
Occupational subtotal: $n = 35$ (50.7%)	Alive	19	12	0	1	32
	Dead	2	0	0	1	3
	Total	21	12	0	2	35
	Fatality rate	9.5%	0.0%	—	50.0%	8.6%
Nonoccupational						
Circumstance						
1. Suicides: $n = 13$ (18.8%)	Alive	0	0	0	0	0
	Dead	13	0	0	0	13
	Total	13	0	0	0	13
	Fatality rate	100.0%	—	—	—	100.0%
2. Poisoning: $n = 18$ (26.1%)	Alive	7	0	9	0	16
	Dead	2	0	0	0	2
	Total	9	0	9	0	18
	Fatality rate	22.2%	—	0.0%	—	11.1%
3. Traffic accident: $n = 3$ (4.3%)	Alive	0	0	0	3[b]	3
	Dead	0	0	0	0	0
	Total	0	0	0	3	3
	Fatality rate	—	—	—	0.0%	0.0%
Nonoccupational subtotal: $n = 34$ (49.3%)	Alive	7	12	9	3	31
	Dead	15	0	0	0	15
	Total	22	12	9	3	46
	Fatality rate	68.2%	0.0%	0.0%	0.0%	32.6%

(Continued on next page)

TABLE 2
Distribution of individual cases by route, circumstance, and clinical outcome of exposure *(Continued)*

	Outcome	Oral	Inhalation	Intravenous	Direct	Total
II. Human Studies: $n = 116$ (62.7%)						
1. Occupational study: $n = 42$ (36.2%)	Alive	0	42	0	0	42
	Dead	0	0	0	0	0
	Total	0	42	0	0	42
	Fatality rate	—	0.0%	—	—	0.0%
2. Therapeutic study: $n = 74$ (63.8%)	Alive	73	0	1	0	74
	Dead	0	0	0	0	0
	Total	73	0	1	0	74
	Fatality rate	0.0%	—	0.0%	—	0.0%
Experimental study subtotal: $n = 116$ (100%)	Alive	73	42	1	0	116
	Dead	0	0	0	0	0
	Total	73	42	1	0	116
	Fatality rate	0.0%	0.0%	0.0%	—	0.0%
Total: $n = 185$ (100%)						
	Alive	99	54	10	4	167
	Dead	17	0	0	1	18
	Total	116	54	10	5	185
	Fatality rate	14.7%	0.0%	0.0%	20.0%	9.7%
	Percent cases	62.7%	29.2%	5.4%	2.7%	100%

[a]Dermal. [b]Eye. [c]45% body burn.

exposure, through eye conjunctiva, only caused local tissue irritations. However, dermal exposure can lead to systemic effects when the skin barrier is broken, such as in one case of a severe body burn. Headache, collapse, hypotension, nausea, and vomiting were reported after all routes.

Hypotension was the most commonly reported health effect across all the routes of exposure to sodium azide/hydrazoic acid: 85 cases in the oral exposure, 24 cases in the inhalation exposure, 10 in the intravenous exposure, and 1 in the dermal exposure. The time interval between the exposure and report of hypotension varied from 1 minute to 30 hours in the oral exposure group. Cases with an interval of greater than 1 hour (range from 1 hour 20 minutes to 30 hours) had decreased mental status, coma, seizures, tachypnea, arrhythmia, asystole, or metabolic acidosis. For the only case of dermal exposure with extensive burns, the interval was 1 hour. All of the cases with an interval between exposure and reported hypotension of greater than 1 hour died. For both the respiratory and intravenous exposure, the interval was much shorter, ranging from 3 minutes to a half hour for inhalation and 5 minutes for intravenous exposure.

Cases with direct eye exposure presented only ocular findings and no hypotension or other systemic findings. Cases with oral, inhalational, or intravenous exposure presented systemic signs of hypotension, headache, collapse, nausea, and vomiting. Only those who inhaled sodium azide reported respiratory symptoms (cough, wheezing, and choking). These cases also reported weakness and unsteadiness. The orally exposed cases presented a wider spectrum of symptoms and signs, including more severe neurologic, gastrointestinal, cardiovascular, respiratory, and metabolic effects. These cases most likely represented higher doses by the oral route. After dermal exposure with extensive burns, effects included hypotension followed by metabolic acidosis.

Early signs and symptoms of sodium azide exposure included hypotension, palpitation, tachycardia, dyspnea, headache, decreased mental status, collapse, weakness, unsteadiness, dizziness, sweating, hyperthermia, paleness, nausea, vomiting, diarrhea, and transient loss of vision within minutes of exposure. More severe and fatal toxic effects had later onsets within a range of an hour to several days. These effects included hypothermia, seizure, coma, cardiac arrhythmia associated with electrocardiogram (EKG) changes, chest pain, pulmonary edema, oliguria, metabolic acidosis, and cardiopulmonary failure.

Of the 38 primary references, 18 gave information about exposure and health effect. We used these data to develop a model that describes the relation between specific exposure dosage and specified health effects (Figure 1). All the publications reported oral and acute exposures, except Black et al.'s experimental study (oral acute and chronic exposure) (Black 1954). The amount of sodium azide exposure determined its toxicity. Doses for adverse health events that did not result in death varied from 0.01 mg/kg to 2 mg/kg, whereas lethal doses were greater than 10 to 13 mg/kg. More severe symptoms and signs of acute intoxication were reported with higher exposure doses (Figure 1).

TABLE 3
Health effects of sodium azide and hydrazoic acid in human by organ systems

	Route									
	Oral		Inhalation		Intravenous		Direct contact (Eye)		Dermal	
Health effects	No.	Onset	No.	Onset	No.	Onset	No.	Onset	No.	Onset
General										
Headche	4	5 to 20 min	24	—	6	—	—	—	—	—
Pounding in the head	1	—	—	—	—	—	—	—	—	—
Weakness	—	—	17	2 min	—	—	—	—	—	—
Unsteadiness	—	—	10	—	—	—	—	—	—	—
Dizziness	6	—	2	20 min	—	—	—	—	—	—
Sweating	3	5 to 20 min	1	2 min	—	—	—	—	—	—
Hypothermia	3	4.5 h	—	—	—	—	—	—	—	—
Paleness	2	5 to 20 min	1	2 min	—	—	—	—	—	—
Cyanosis	1	—	—	—	—	—	—	—	—	—
Restlessness	1	5 to 20 min	—	—	—	—	—	—	—	—
Hyperthermia	1	10 min	—	—	—	—	—	—	—	—
Vertigo	—	—	1	2 min	—	—	—	—	—	—
Fever and chills	—	—	1	24 h	—	—	—	—	—	—
Neurological										
Collapse	12	5 min to 1 h	1	5 min	2	—	—	—	—	—
Decreased MS	7	5 min to 4.5 h	—	—	—	—	—	—	—	—
Comatose	4	1 to 30 h	—	—	—	—	—	—	—	—
Seizure	4	0.5 to 3.2 h	—	—	—	—	—	—	—	—
Fasciculation	1	—	—	—	—	—	—	—	—	—
Cardiovascular										
Hypotension	85	1 min to 30 h	24	3 to 30 min	10	5 min	—	—	1	1 h
Palpitation	6	3 to 5 min	21	—	—	—	—	—	—	—
Tachycardia	9	5 min to 1 h	1	2 h	—	—	—	—	—	
Arrhythmia	6	1 to 13 h	—	—	—	—	—	—	—	—
Bradycardia	4	2 to 8 h	1	—	—	—	—	—	1	14 h
Arrest	5	30 h	—	—	—	—	—	—	1	14 h
EKG changes	4	—	—	—	—	—	—	—	—	—
Myocardial Infarction	2	48 to 72 h	—	—	—	—	—	—	—	—
Pulmonary										
Tachypnea	5	1.5 to 30 h	—	—	—	—	—	—	—	—
Dyspnea	3	5 min to 24 h	5	—	—	—	—	—	—	—
Cough	—	—	1	—	—	—	—	—	—	—
Wheezing	—	—	2	—	—	—	—	—	—	—
Choking	—	—	2	—	—	—	—	—	—	—
Respiratory failure	2	6 h	—	—	—	—	—	—	—	—
Pulmonary edema	2	4.5 h	—	—	—	—	—	—	—	—
Gastrointestinal										
Nausea	5	5 min to 1.5 h	6	2 min	3	—	—	—	—	—
Vomiting	5	5 to 20 min	2	—	3	—	—	—	—	—
Diarrhea	3	5 to 20 min	—	—	—	—	—	—	—	—
Cramps	—	—	—	—	1	—	—	—	—	—

(Continued on next page)

TABLE 3
Health effects of sodium azide and hydrazoic acid in human by organ systems *(Continued)*

	Route									
	Oral		Inhalation		Intravenous		(Eye) Direct contact		Dermal	
Health effects	No.	Onset	No.	Onset	No.	Onset	No.	Onset	No.	Onset
Urinary										
Oliguria	1	4 h	—	—	—	—	—	—	—	—
Incontinence	1	5 min	—	—	—	—	—	—	—	—
Ear, Nose, and Throat										
Blurred vision	—	—	1	—	4	—	1	—	—	—
Eye irritation	—	—	3	—	—	—	2	—	—	—
Oral mucosa irritation	1	—	5	—	—	—	—	—	—	—
Nasal swelling	—	—	2	—	—	—	—	—	—	—
Transient loss of vision	2	10 min to 1 h	—	—	—	—	—	—	—	—
Red eye	—	—	1	—	—	—	1	—	—	—
Tearing	—	—	—	—	—	—	1	—	—	—
Photophobia	—	—	—	—	—	—	1	4 h	—	—
Corneal scar	—	—	—	—	—	—	1	—	—	—
Head and ear pressure	—	—	1	—	—	—	—	—	—	—
Other										
Metabolic acidosis	5	4 to 5 h	—	—	—	—	—	—	1	—
Flaccidity	2	2 h	—	—	—	—	—	—	—	—
Laryngeal dyspnea	1	—	—	—	—	—	—	—	—	—
Knee swelling	—	—	1	—	—	—	—	—	—	—
Blue spots on both legs	—	—	1	—	—	—	—	—	—	—
Facial flushing	—	—	1	—	—	—	—	—	—	—
Polydypsia	1	—	—	—	—	—	—	—	—	—

The lowest reported adverse human health effect was hypotension at 0.01 mg/kg, followed by decreased mental status, vomiting, nausea, and diarrhea at 0.04 mg/kg, and headache, sweating, collapse, palpitation, and temporary loss of vision at 0.07 mg/kg. Severe health effects such as seizure, coma, pulmonary edema, flaccidity, metabolic acidosis, arrhythmia, bradycardia, and asystole were observed only following doses of 10 mg/kg or above, the minimal lethal dosage. Hypotension had the widest dosage exposure spectrum (0.004 to 786 mg/kg), followed by impaired mental status (0.04 to 786 mg/kg), collapse (0.07 to 786 mg/kg), and vomiting (0.04 to 129 mg/kg).

Some publications reported trials of specific antidotes, attempts to remove the toxin, and treatment of specific health complications. Specific poisoning treatments, included amyl nitrite, sodium nitrite, and sodium thiosulfate, meant to induce formation of methemoglobinemia were unsuccessful (Lambert, Meyer, and De Leenheer 1995; Emmett and Ricking 1975). Ipecac, activated charcoal, gastric lavage, and peritoneal dialysis have been used to attempt to remove the azide without success. Severe complications (cardiac, respiratory, neurological, etc.) have been treated therapeutically. Diagnostic procedures have been undertaken to rule out other causes. As with all intoxications, the first step is to prevent continuing exposure and to treat the patient.

Autopsies revealed the following macroscopic pathological findings: (a) pulmonary congestion/edema; (b) gastric mucosa erythema/edema; (c) liver congestion/yellowish spots; (d) brain, bronchial tree, kidney, pelvic organs, small intestine congestion/swelling; (e) soft myocardium; (f) pleura and epicardium petechia; (g) frothy, pinkish fluid from bronchial tree; (h) brownish color blood; and (i) purple and bluish lividities. After microscopic examination, the pathological findings were: (a) alveolar interstitial edema and polymorphonuclear infiltration; (b) cardiac cell congestion; (c) fatty liver degeneration; (d) distal ileum mucosal hemorrhage and erosion; (e) extensive vascular congestion and tissue edema; and (f) liver cells peliosis (purpura) (Klein-Schwartz et al. 1989; Howard et al. 1990; Lambert, Meyer, and De Leenheer 1995; Emmett and Ricking 1975; Albertson, Reed, and Siefkin 1986; Herbold et al. 1995; Marquet, Clement, and Lotfi 1996; Kozlicka-Gajdzinska and Brzyski 1966; Klug and Schneider 1987; Kayser 1928). No pathognomonic findings were found in autopsies. Pathologic findings of sodium azide intoxication were also mainly

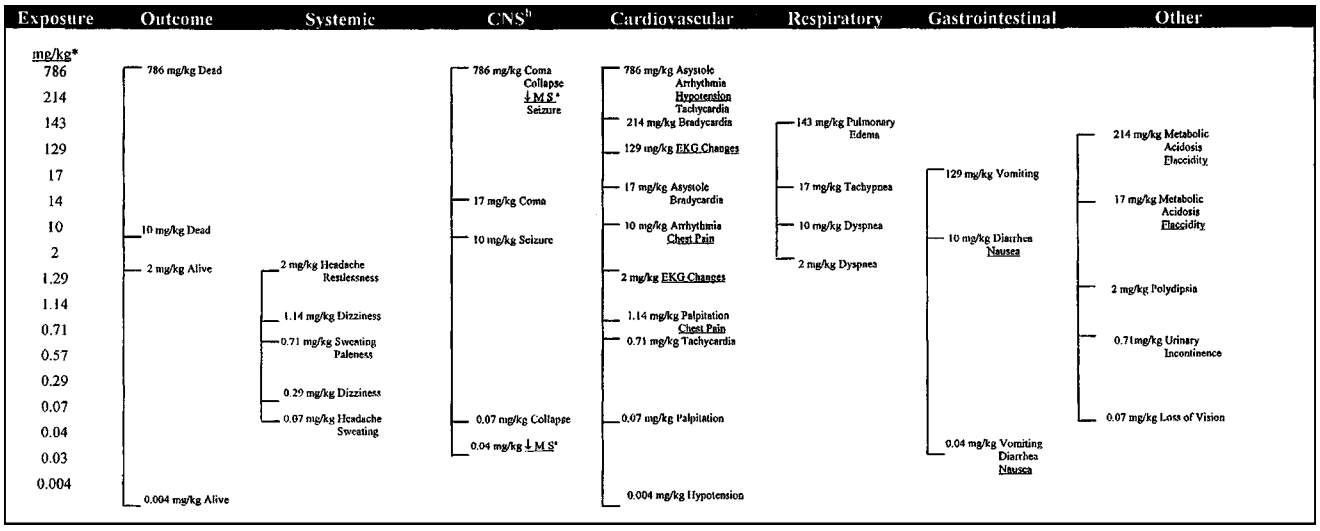

FIGURE 1

Dose-health effect diagram. *Note:* Exposures have been expressed in mg/kg by assuming a 70-kg person when total dose was given without body weight. [a]Decreased mental status. [b]Central nervous system.

nonspecific, such as edema and congestion of the targeted organs.

Most of the poisoning incidents related to laboratory or health care settings. Confusion between sodium azide solutions and water or other clear solutions explains this relationship, particularly given the tasteless and colorless properties of sodium azide solution. Half of the reported suicides obtained their sodium azide through their professional or academic involvement with a laboratory (Klein-Schwartz et al. 1989; Albertson, Reed, and Siefkin 1986; Marquet, Clement, and Lotfi 1996; Klug and Schneider 1987; Abrams, el-Mallakh, and Meyer 1987; Wollenek 1989; Peclet and Ponton 1991).

Occupational exposures other than the laboratory setting occurred among azide industry workers, warehouse, and cargo transport workers (Rippen et al. 1996; Trout et al. 1996; Weiss 1996; Gobbi 1967; Lamm et al. 1999; Gesell and Otton 1997). Five cases (two from US cargo transport workers and three from the Italian azide industry) had been exposed through inhalation (Weiss 1996; Gobbi 1967). Health complaints of the three cases exposed in the azide industry resolved after the introduction of personal protective measures, such as mask and gloves (Gobbi 1967).

Two occupational studies in a sodium azide manufacturing factory showed that the health complaints of workers exposed to sodium azide were mainly mild headaches, palpitations, and hypotensive episodes (Rippen et al. 1996; Trout et al. 1996). Personal breathing zone air monitoring revealed exposure to sodium azide (up to 1.7 mg/m^3) at levels greater than the NIOSH REL of 0.3 mg/m^3 in the blending and packing area of the plant. Only one of nine samples of hydrazoic acid was below the level of the REL (0.10 ppm). During medical evaluation, only one worker met the case definition for hypotension. After introduction of preventive measures, such as engineering controls, health surveillance monitoring, and protective equipment use, complaints decreased. Respirators must protect against both particulate sodium azide and vaporous hydrazoic acid. Three cases of chemical keratitis were reported among persons exposed to sodium hydroxide, a by-product of the sodium azide, following airbag deflation in traffic accidents (Ingraham, Perry, and Donnenfeld 1991; Smally et al. 1992; White et al. 1995).

The US EPA Integrated Risk Information System (IRIS) specifies an oral reference dose (RfD) of 0.004 mg/kg per day, based on data from rats. The Agency believes that an RfD is an estimate of a daily human exposure that is likely to be without an appreciable risk of deleterious effects over a lifetime, including the sensitive subgroup (US EPA 2000). In this review, the lowest adverse health effect was hypotension, which occurred after approximately 0.004 mg/kg exposure.

DISCUSSION

Human health effects of sodium azide were first reported in 1927, but to date, the mechanism of toxicity remains unknown. The basic physiological effect of sodium azide is vasodilatation, resembling nitroglycerin and other nitrites. The stimulation of carotid chemoreceptors can explain hypotension in part. In part, sodium azide may have a vasodilator action, like that of nitric oxide. Some authors argue that lethality is due to formation of nitric oxide after conversion of sodium azide (Smith and Wilcox 1994; Smith et al. 1991).

Rapid onset of hypotension occurs within minutes (usually up to 5 minutes) and may be accompanied or followed up with headache and associated symptoms such as dizziness, weakness, blurred vision, palpitation, tachycardia, shortness of breath, and

sudden collapse (faint) that results in full recovery. These symptoms and signs are consistent with sudden lowering of blood pressure. In contrast, late development of hypotension (>1 hour), usually preceded or accompanied central nervous system (CNS) toxicity (seizure, decreased mental status, and/or coma), cardiac toxicity (tachycardia, arrthymia, bradycardia, or a systole), tachypnea, and metabolic acidosis. Late onset of hypotension constitutes an ominous sign of death. The difference in the onset of hypotension might be related to the dosage and route of exposure. Cases exposed to doses of 700 mg or above and those with oral or direct contact exposures (45% body burn) developed late onset of hypotension.

Biochemical studies show that sodium azide inhibits cytochrome oxidase and interferes with cellular respiration (Trochimowicz 1990). These properties do not explain the hypotensive symtoms. In severe sodium azide intoxication, the clinical presentation resembled cyanide intoxication with metabolic acidosis, severe hypotension unresponsive to fluids and vasoconstrictors, and seizures (Hitt 1992). The lack of success with the use of specific antidotes for acute cyanide intoxication (amyl nitrite, sodium nitrite, and sodium thiosulfate) supports the idea that sodium azide acts differently from cyanide. Other emergency measures generally applied for detoxification, such as gastric lavage and ipecac administration, have not been helpful, probably because rapid absorption of sodium azide and already occurred in the gastrointestinal tract and respiratory tract before the initiation of treatment. Because no specific treatment is available for sodium azide intoxication, the best strategy is to avoid sodium azide toxicity by identifying the populations at risk and implementing preventive measures.

Based on the clinical literature, sodium azide mostly affects adults (99% of the cases). The clinical outcome of sodium azide exposure depends on the circumstances, route, and dose. The degree of health effects varied from mild to severe. Hypotension, headache, nausea, and vomiting were common features by each route of exposure. Vomiting was rare after workplace exposures. Direct contact posed the least toxicity, only causing local tissue irritation. The most common health effects after inhalational exposures were headache, weakness, unsteadiness, and dizziness, accompanied by hypotension and palpitation. No fatal cases were reported after inhalation exposure. More severe symptoms, such as collapse, decreased mental status, and tachycardia, were observed after oral exposure.

Occupational exposure accounted for 65% of the reported human exposure to sodium azide. All the fatalities had oral exposures, either intentional ingestions, such as suicide cases, or unintentional exposures, such as accidents and poisonings. The lowest leathal dose in humans was 10 to 13 mg/kg.

Although concerns of potential environmental exposures have increased, almost no evidence supports sodium azide as an environmental health hazard for the public. Emergency measures should be applied in cases of sodium azide spills in the workplace or in the environment, such as evacuation and ventilation of the contaminated place. Potential hazards to automobile occupants consist of by-products from combustion of sodium azide rather than the sodium azide itself. The nitrogen gas is potentially contaminated with trace amounts of sodium oxide, which may hydrolze to sodium hydroxide. The majority of this material is retained within the airbag system by high-efficiency filtration systems. The frequency of associated health effects of transient ocular or nasal irritations following airbag deflation may be reduced by appropriate ventilation of the car compartment.

Prevention is the best measure to avoid the health risk of sodium azide from occupational and potential environmental exposure. In the sodium azide production and airbag manufacturing industry, appropriate engineering controls, institution of administrative measures, and personal protective equipment are examples of preventive measures. In the laboratory environment, protective measures are access control, better labeling or coloration of the products containing sodium azide, and stricter enforcement of laboratory regulations. Other preventive measures include education about the physical and chemical properties of sodium azide and its health effects.

In summary, people working in laboratories that use sodium azide or people involved in the health care settings are at highest risk of fatal sodium azide intoxication. Intentional, as well as accidental, ingestions of sodium azide are the main causes of acute sodium azide intoxications. Such cases have been known since 1927 and have still been reported in 1999. Measures to prevent future deaths and intoxications should gear toward the laboratory workers and other workers with greater potential exposure to sodium azide.

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