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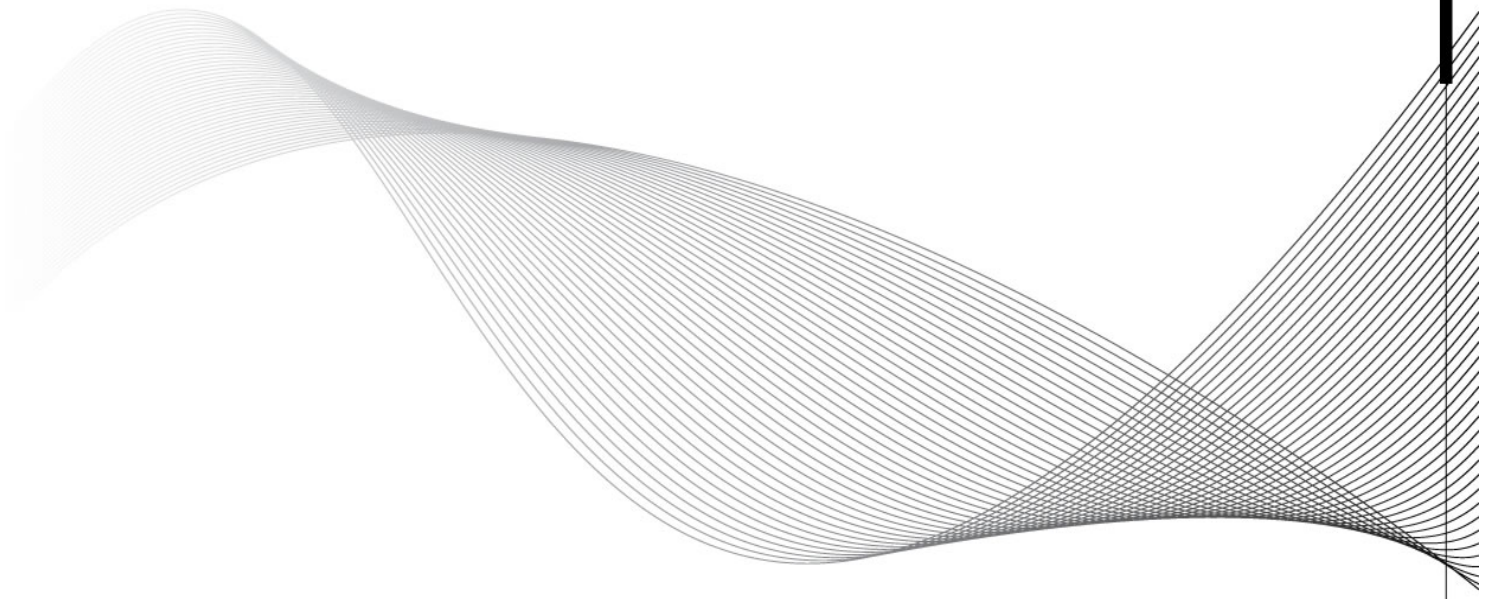

Recommendation from the Scientific Committee on Occupational Exposure Limits for sodium azide

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8 hour TWA:	**0.1 mg/m³**
STEL (15 mins):	**-**
Notation:	-
BLV:	-

Substance identification

Sodium azide:

Na^+

$N^-{=}N^+{=}N^-$

Synonyms: Hydrazoic acid, sodium salt
EC No.: 247-852-1
Annex I Index No.: 011-004-00-7
EU Classification: T+; R28 - R32 - N; R50-53
CAS No.: 26628-22-8
MWt: 65.01
Conversion factor (20 °C, 101 kPa): not applicable

Physico-chemical properties

Sodium azide is a colourless, crystalline solid, manufactured as a very fine powder (Rippen HE at al., 1996).

Solubility in cold water: 40.17 g/100 g – in presence of water it is readily transformed to hydrazoic acid, the vapour of which may be present whenever the salt is handled. It is also soluble in ammonia but not in ether.

Sodium azide decomposes on heating, emitting toxic fumes (HSE, 2000).

Crystalline sodium azide is explosive.

Specific gravity of sodium azide: 1.846 g/cm³ at 20°C (ACGIH, 2001).

1. Occurrence/use and occupational exposure

Sodium azide is used in organic synthesis, in production of explosives, as a preservative in aqueous laboratory reagents, as a gas generating chemical in automobile air bags and seat ejectors of jet planes. It used to have limited use in the clinical management of hypertension in the 1950s. The production rate in the EU is in excess of 1000 tonnes per annum (HSE, 2000).

2. Health significance

2.1. Toxicokinetics

2.1.1. Human data

No quantitative data are available regarding the absorption, distribution, metabolism and elimination of sodium azide in humans.
It is reported to be quickly absorbed from the gastrointestinal tract. Hypotension developed within 45-60 sec after ingestion of 1.3 mg dose (Black et al., 1954).
The degree of skin penetration via undamaged skin is not clear. (Chang and Lamm, 2003).

2.1.2. Animal data

The azide anion appeared within 5 min in the plasma of rats following oral administration of 40 mg/kg sodium azide. After 24 h, no more azide could be detected in either plasma or tissue and only 7.9 µg were excreted in the 24 h urine. No sodium azide was detectable in the faeces or in exhaled air, suggesting a rapid and complete metabolism of this substance. (Lee, 1982).
The data on dermal absorption are contradictory (Bassendowska and Kowalski, 1961; Bassendowska et al., 1965; Potocar et al., 1985; see also acute dermal toxicity).
Sodium azide is reported to be quickly absorbed from injection sites and from the respiratory tract (Bassendowska, 1962; Reinhardt and Brittelli, 1981).
Sodium azide is mainly metabolised in the liver (Trochimowicz, 1990). The main metabolite in the liver is nitric oxide (Smith et al., 1991; Marquardt and Schäfer 1994). Sodium azide penetrates the blood-brain barrier (Smith et al., 1991). Azide anions may be metabolised to nitric oxide (NO) also in the CNS (HSE, 2000). In aqueous solution, it rapidly transforms into hydrazoic acid (CAS no. 7782-79-8), which may be responsible for the irritating effects attributed to sodium azide (Graham et al., 1948, cit. HSE, 2000; Haas and Marsh, 1970).

2.1.3 Biological monitoring

Biological monitoring is not in use, existing experimental blood tests are too insensitive to detect anticipated blood sodium azide levels (Rippen at al., 1996).

2.2. Acute toxicity

2.2.1. Human data

During clinical treatment, acute oral ingestion of 1.3 mg sodium azide rapidly (45-60 s.) decreased the blood pressure of hypertensive patients for 10-15 minutes, but had only minor effects on normotensive individuals. Therefore, a difference in the relative sensitivity

of normotensive and hypertensive individuals towards sodium azide is assumed (Black et al., 1954).
Most human acute toxicity data are coming from poisonings caused by accidental or intentional ingestion of sodium azide. The symptoms - sweating, headache, increased pulse rate, decreased blood pressure, blurred vision, faintness – were rapidly reversible after ingestion of 5 to 10 mg sodium azide (0.09 to 0.18 mg/kg) in one case, while in another case, the parameters reached normal levels again after 1 h of ingestion of 50-60 mg sodium azide. (Richardson et al., 1975).
In a fatal intentional case (no dose reported) oedema of the brain (severe) and the lungs (moderate), mild congestion of the abdominal organs, diffuse redness of the mucous membranes, fatty degeneration in the liver were also reported (Wollenek, 1989).
Acute hypotension, nausea, vomiting, and weakness were reported in two case studies, in which workers were exposed by inhalation to high concentrations of sodium azide dust (no figures given) during cleaning activities. Subsequently, both developed persistent reactive airway dysfunction syndrome (RADS - Weiss, 1996; see also section "irritation and corrosivity").
Massive exposure caused by a sodium azide canister explosion resulted in severe systemic toxicity and finally led to death (Pham et al., 2001). The exposed patient developed hypothermia, hypotension, bradycardia and a profound metabolic acidosis leading to death about 12 h after exposure.
(Chang and Lamm, 2003) cite 5 cases of dermal exposure in their review, of these one died and the other 4 showed no symptoms of intoxication. The one that died had 45% burns and presumably massive exposure via damaged skin.

2.2.2. Animal data

Inhalation exposure
Inhalation exposure of rats, mice, guinea pigs or cats to sodium azide at lethal concentrations caused hypothermia, convulsions, dyspnoea, palsy and hyperventilation followed by apnoea. At necropsy, both liver and kidneys were congested and the liver was bloody, while all other organs were anaemic (Fairhall et al., 1943; Hildebrandt and Schmidt, 1937).

Oral exposure
The substance is very toxic in acute oral studies, with an LD_{50} of 27 mg/kg in mice (Graham, 1949). In rabbits, an oral dose of 3 to 10 mg/kg caused haematuria, tachycardia and a 40 to 60% reduction in blood pressure, which lasted at least 1 hour (Roth et al., 1956, cit in HSE, 2000).

Dermal exposure
No dermal LD50 values are available in the scientific literature. Bassendowska and Kowalski (1961) concluded that the dermal lethal dose (LD) of sodium azide for rabbits is 18-21 mg/kg, based on a dermal irritation study, where a single rabbit, exposed to 60 mg substance via the skin, died after 6 hours. Another rabbit exposed to 40 mg (13 mg/kg), survived for 24 hours.
In a later study Bassendowska et al. (1965) established a 60 mg/kg dermal LD for rats.
In a skin irritation study Potocar et al. (1985) reported the death of 3 of the 6 rabbits in the test group for sodium azide. Four 3x3 cm patches with 0.5 g solid substance each

(altogether 2 g) were placed on the skin of each animal. Two patches were kept for 1 hour and two for 4 hours. The animals were followed for 7 days. The weight of the animals was 2-4 kg, so a 500-1000 mg/kg individual dose can be estimated, depending on the weight.
Unfortunately, no further data are given regarding the time of the deaths of the animals. As after 4 hours of exposure corrosion was detected on the skin, it cannot be excluded that the death of the animals was caused by penetration of sodium azide through the damaged skin.
Regarding dermal toxicity, however, it can be concluded from the study of Potocar et al. (1985), that 3 surviving animals were exposed to 500-1000 mg/kg sodium azide for 1 hour and then to half of that dose for three additional hours on their skins. These data do not support the low dermal LD value of 20 mg/kg for rabbit mentioned in the Bassendowska studies.

Other routes of exposure
After subcutaneous administration of sodium azide dissolved in water an LD50 of 45.1 mg/kg was established in rats and 23.06 mg/kg in mice (Bassendowska and Kowalski, 1961).
Intratracheal administration of sodium azide dissolved in water resulted in an LD50 of 47.5 mg/kg in rats (Bassendowska and Kowalski, 1961).
Analogous to humans, application of 0.1 mg sodium azide (i.v.) markedly decreased the blood pressure of hypertensive rats (from 180-200 mm Hg to 120 -130 mm Hg) for a period of 30-45 minutes. However, it did not cause hypotensive effect on normotensive rats (Black et al., 1954).

2.3. Irritation and corrosivity

Sodium azide is not an irritant but is rapidly hydrolysed to hydrazoic acid in the acidic environment of mucous membranes and the tracheobronchial tree (Weiss, 1996).

2.3.1. Human data

10 workers potentially exposed to sodium azide and hydrazoic acid for 1 to 16 years complained of mild eye and nose irritation, but it is unclear what concentrations of sodium azide initiated these effects. Air concentrations of hydrazoic acid, measured over several days, were between 0.3 and 3.9 ppm (Graham et al., 1948, cit. HSE, 2000).
Among laboratory personnel working with sodium azide Haas and Marsh (1970) reported nasal irritation, attributed to hydrazoic acid vapour concentration of 0.5 ppm measured in the air.
Self-reported "red or irritated" eyes during the past 5 workdays occurred more frequently in 41 workers exposed to sodium azide (mean concentration in air: 0.23 mg/m^3, range: 0 – 0.93 mg/m^3, personal sampling, hydrazoic acid concentration was not measured) compared to 42 controls (85 % versus 41 %) (Miljours and Braun, 2003).
In the study of Trout et al. (1996) no irritation symptoms were reported among the 11 workers exposed up to 0.69 mg/m^3 sodium azide concentration, with a simultaneously measured hydrazoic acid concentration up to 0.07 ppm in the air. The personal breathing zone sample results for the same workers were up to 1.7 mg/m^3 sodium azide and up to 0.1 ppm hydrazoic acid.
In the Rippen et al. (1966) study eye or throat irritation symptoms occurred occasionally

during the 9 months follow up and do not seem to be in close connection with the sodium azide air concentrations measured. At the beginning of the study none of the 65 workers reported irritation symptoms (air sodium azide: 1-7.5 mg/m^3, hydrazoic acid: 0.45 – 2.81 ppm). Three months later 4 cases of eye irritation and 1 case of sore throat were recorded (average air sodium azide below 1 mg/m^3) and in the next two months again none irritation symptom was reported. At the end of the study (average air sodium azide below 0.5 mg/m^3) only 1 case of eye irritation was recorded among the 65 workers.
Persisting reactive airway dysfunction was reported in two case studies, in which workers were exposed by inhalation to high concentrations of sodium azide dust (no figures given) during cleaning activities (Weiss, 1996; see also section "acute toxicity – human data").

2.3.2. Animal data

No signs of dermal or conjunctival irritation appeared up to 10 hours (when the animals died) after the application of 4x10 mg sodium azide on 4 places (2 of them scarified) on the skin and simultaneously 20 mg into the conjunctival sac of 2 rabbits. (Bassendowska et al. 1961).
No sign of conjuctival irritation appeared after 24 hours when 20 mg sodium azide was applied into the conjunctival sac of a single rabbit. Another rabbit exposed to 60 mg substance via the skin, died after 6 hours without any sign of dermal irritation. A third rabbit exposed to 40 mg (13 mg/kg) sodium azide for 24 hours on the skin, showed local reaction (hyperemia, subepithelial exudation). (Bassendowska et al., 1961).
Dermal (semi-occlusive and occlusive) exposure to 0.5 g/patch solid sodium azide for 1 hour did not produce signs of local irritation in rabbits, whereas exposure for 4 hours was corrosive (Potokar et al., 1985). However, the authors concluded, that tests for corrosiveness should be carried out with an exposure time of 1 hour.

2.4. Sensitisation

No data were reported in HSE (2000) and none has been found since.

2.5. Repeated dose toxicity

2.5.1. Human data

Oral exposure
In a clinical study 9 normotensive individuals ingested 1.3 mg sodium azide three times/day (3.9 mg/day, or 0.056 mg/kg/day) for 10 days, without experiencing "sustained effect" on blood pressure (Black et al., 1954).
No evidence of kidney, heart and liver damage was detected by routine clinical examinations in 30 hypertensive patients treated with oral doses of 0.65 to 3.9 mg (up to approximately 0.056 mg/kg/day) sodium azide daily, for 5 days to "more than 2 years". The blood pressure of 25/30 patients decreased towards the normal level. Some of the patients developed increased sensitivity to sodium azide during repeated treatment, requiring the reduction of the dose (Black et al., 1954).

Inhalation exposure - occupational
Graham et al. (1948, zit. HSE 2000).

Detailed medical examinations were performed on 10 workers potentially exposed to sodium azide and hydrazoic acid for 1 to 16 years. No pathological changes were observed, although 'definite' hypotension was noted. The workers complained of headaches, palpitation, periods of weakness and mild eye and nose irritation, but it is unclear what concentrations initiated these effects

Trout et al. (1996).

11 workers were evaluated in a sodium azide production plant. The most often reported symptoms during the 6 months period prior to the evaluation were headaches (10/11), increased heart rate and palpitation (9/11), low blood pressure (9/11). For exposure assessment, at the time of the 24-hour evaluation survey 10 area samples (with results ranging from not detectable to 0.69 mg/m^3 sodium azide) and 28 personal breathing zone (PBZ) samples were collected. Air sodium azide concentration of 7/28 PBZ samples exceeded the actual TLV of 0.3 mg/m^3, the highest value being 1.7 mg/m^3. During the simultaneous medical evaluation, 4/11 workers reported mild headaches. Two of them worked in the blending and packaging area, where the highest of all (1.7 mg/m^3) PBZ air concentration was measured - for one of these workers 3 consecutive PBZ sample results measured within 3 hours were: trace, 0.31 and 0.43 mg/m^3, respectively. Two of the workers with headache, however, were working in other areas, where PBZ sample results were 0 - 0.23 mg/m^3. Blood pressure monitoring revealed one case of hypotensive episode occurring during the examination period, in the worker with PBZ air sample result of 1.7 mg/m^3 sodium azide, but without complaints.

Rippen et al. (1996).

The occupational health and hygiene situation was evaluated in a sodium azide production plant, where the 65 employees had reported headaches, rapid pulses, the perception of lowered blood pressure and mental status changes, such as disorientation and near faints. Sodium azide air samples measured ranged from 0.20 - 5.87 mg/m^3.

At the beginning of the study 1.0 – 7.5 mg/m^3 sodium azide concentration was measured in the workplace air. Twelve of the 65 workers reported headache and none blood pressure changes or eye and throat irritation at this exposure level. Blood pressure surveillance system revealed that cross-shift decreases in the mean arterial blood pressures (-3.6 mmHg) did not reach the level regarded as significant change (NIOSH: 13.3 mmHg).

To assess the effect of possible higher short term azide exposure levels on the blood pressure, 12 short term (15 min) exposure air samples were collected for individual workers. Six of the measures exceeded 0.3 mg/m^3 sodium azide (range: 0.36-1.49); the other 6 were less than 0.3 mg/m^3 sodium azide (range: 0.01-0.15). The means of pre-exposure versus post exposure blood pressures and heart rates were not significantly different in the groups with exposure levels either below 0.3 mg/m^3, or above 0.3 mg/m^3. However, the mean pre-exposure blood pressure in the group with the higher exposure levels (>0.3 mg/m^3) was significantly lower than that in the group with the lower exposure levels (<0.3 mg/m^3).

After 5 months of monitoring, the hygienic measures introduced resulted in a constant decrease in the air sodium azide concentration. The number of workers reporting headache decreased from 12 to 1, while the cases with blood pressure changes reported varied between 0 and 3.

Miljours and Brown (2003).

The occupational neuropsychotoxicology of sodium azide was investigated annually, for

three years in 41 sodium azide exposed workers in a chemical production plant, compared to 42 unexposed ones working in the same plant. The duration of exposure of the workers varied between 5 and 30 years. In the past, the legal limit of 0.3 mg/m^3 had often been exceeded. Personal air samples collected from each of the workers at the beginning of the survey indicated sodium azide concentrations ranging from 0 to 0.93 mg/m^3, mean 0.23 mg/m^3.
The systolic blood pressure was significantly lower in the exposed workers (125 mmHg versus 131 mmHg in the controls). Acute self-reported symptoms of toxicity during the past 5 workdays (headache, vertigo, nausea, fatigue, heart palpitation, eye irritation) were significantly more frequent in the exposed workers compared to the unexposed ones, however, the controls were affected quite often too. For example, 34 % of the controls had headache and 41 % of them had eye irritation versus 85 % in the exposed ones. These symptoms were reported with significant differences to controls, but with decreasing incidence in the second year survey. In the third year, only heart palpitations and eye irritation were reported significantly more often. Only one chronic symptom – tremor of the hands – was significantly increased for the exposed workers in year 1 (15 % versus none in the controls) and 3, but not in year 2. No explanation was offered for this difference by the authors. Nevertheless, the authors suggested to include a test for trembling in future studies on chronic sodium azide exposure. The results of psychological and neuropsychological tests did not differ between both groups, except for the impairments of mood in the exposed group

2.5.2. Animal data

Oral studies
NCI (1981) Study No. 5650.08 (cit. EPA):
90-day gavage (distilled water) study with rats (10/sex/group) exposed to 0, 1.25, 2.5, 5.0, 10 or 20 mg/kg/day sodium azide, 5 days/week. Nearly total mortality occurred at the 20 mg/kg dose, no deaths occurred at other doses. A trend of reduced weight gain was seen in the 10 mg/kg group. In females slightly elevated mean relative liver weights were measured in all dosage groups, with unknown statistical significance. Histopathology revealed lesions in the brain and lung of the high dose rats that died. Hunched postures were noted among males in the two highest dosage groups and females in the 20 mg/kg group.
NTP (1991) Study TR-389:
In a repeated oral dose study, rats received 0, 5, 10, 20, 40, 80, mg/kg/day sodium azide in water by gavage for 14 days (5 days/week). Deaths occurred with 20 mg/kg/day and above. Clinical findings of toxicity included lethargy and inactivity.
Oral administration of 0, 1.25, 2.5, 5.0, 10 or 20 mg/kg/day sodium azide in water by gavage for 13 weeks, resulted in statistically significant, but non-dose-related, increases in relative liver weights in female rats from all dose groups and 10% reduction of body weight in all treated groups. At the top dose, lethargy and laboured breathing preceded death, when necrosis in the cerebrum and thalamus, congestion, haemorrhage and oedema in the lungs were observed by microscopy. Blood pressure measurements were not made. Thus the LOAEL is 1.25 mg/kg and no NOAEL could be derived from these data.
In a 2-year carcinogenicity study male and female rats were treated with 0, 5, or 10

mg/kg/day sodium azide by gavage. The majority of rats given the 10 mg/kg dose showed clinical signs of systemic intoxication, but convulsions were recorded, coma and death occurred in both groups, given 5 or 10 mg/kg/day dose. Survival significantly decreased in the high dose groups. This was attributed to cardiovascular collapse secondary to brain necrosis. Histopathology revealed that sodium azide induced necrosis in the cerebrum and the thalamus of the brain both in male and female rats. The 2-year study demonstrated a cumulative toxicity from the long-term administration of sodium azide at doses that were not toxic in the short-term studies (NTP, 1991).

Parenteral studies
Rats receiving 0.4 mg/hour sodium azide by infusion for two weeks showed a 26-37% decrease in brain cytochrome oxidase activity in 22 different regions of the brain. The mesencephalic reticular formation and the central amygdala proved to be the most vulnerable. Also the correlative metabolic activity between hippocampal, amygdaloidal and cortical areas were deeply modified. The regional effects found were consistent with azide induced learning and memory dysfunctions (Cada et al., 1995).
In rats s.c. infusion of 1 mg/kg/h sodium azide selectively inhibited the mitochondrial cytochrome c oxidase activity in the brain, which became evident by 7th day of infusion and persisted for about 3 weeks (Bennett et al, 1996).
After 28 days of systemic administration of 0.86 mg/kg/h sodium azide Berndt et al, (2001) demonstrated a significant decrease of cytochrome oxidase activity in the brain and the skeletal muscle.
Similar neuropathological findings were reported by Mettler (1972 – cit Miljours and Braun, 2003) in sodium azide treated primates.
Lalonde et al. (1997) found adverse effects on motor activity and learning in mice injected with 6 or 12 mg/kg sodium azide.
In vitro and in vivo animal experiments demonstrated, that sodium azide impairs the cellular metabolism, by inhibiting phosphorylation (Bogucka and Wojtczak, 1996), glycogenesis (Robertson and Boyer, 1955), and oxidative enzymes like catalase (Nicholls, 1964), peroxidase (Smith and Wilcox, 1994) and cytochrome oxidase (Benneth et al., 1996).

2.6. Genotoxicity

2.6.1. In vitro

Sodium azide is mutagenic in vitro, producing gene mutations in bacteria (NTP, 1991) and mammalian cells (Jones et al., 1980). It induced sister chromatid exchanges, but did not produce chromosomal aberrations in two well-conducted studies using human lymphocytes and Chinese hamster ovary cells (NTP, 1991; Sander et al., 1978). Because of the specific metabolism of sodium azide in bacteria, mutagenicity in Salmonella typhimurium and in Escherichia coli is considered irrelevant for risk assessment (Greim, 2003).

2.6.2. In vivo

Sodium azide was not significantly mutagenic in *Drosophila melanogaster* and did not increase sex-linked recessive lethality (SLRL), (Sadiq et al., 2000). Slightly positive effects occurred in an other SLRL test on *D. melanogaster* (Kamra and Gollapudi, 1979) and

positive effects were observed in a dominant lethal test in the housefly (*Musca domestica*) (Thakur and Mann, 1981).
No studies on mammals are available to adequately assess germ cell effects (Greim, 2003).

2.7. Carcinogenicity

2.7.1. Human data are not available.

2.7.2. Animal data

In a well-conducted carcinogenicity study, no compound-related increases in tumour incidences were observed in rats treated with 0, 5 or 10 mg/kg/day sodium azide, 5d/w for 2 years (NTP, 1991).
Similarly there was no evidence of carcinogenicity in a 2-year study in which rats were fed 100 or 200 ppm sodium azide in the diet for 78 weeks (Weisburger et al., 1981).

2.8. Reproductive toxicity

Fertility
No human data on fertility are available
Animal data
Oral administration of 5 and 10 mg/kg sodium azide for a period of one year (5 d/w) did not cause significant changes in length and frequency of the oestrous cycle of female rats, but increased the number of cycles defined as "unclear" (NTP, 1991).
In the housefly (*Musca domestica),* sodium azide (1mg/ml diet) produced 72.3% infertility. Mating of dosed males with untreated females resulted in 33.1% infertility (Thakur and Mann, 1981).

Developmental toxicity
Human data on developmental toxicity are not available
Animal data
The effects of sodium azide on the foetus have been examined in Syrian hamsters following subcutaneous infusion via osmotic minipumps (Sana et al., 1990 a,b). Embryotoxicity was seen at dose levels that resulted in maternal toxicity (HSE, 2000).
Faqi et al., (2008) studied the developmental effects of sodium azide in rats. Oral doses of 0, 1, 5, or 17.5 mg/kg/day were administered from gestation day 6 through 19. The 17.5 mg/kg/day dose was reduced to 10 mg/kg/day from gestation days 10-12, due to maternal mortality. Reduced gestational body weight and fetal weight were recorded in the dams surviving the high dose treatment. No maternal deaths, clinical signs or body weight effects were seen at 1 or 5 mg/kg/day. No increase in the incidence of malformations and variations were observed at any of the doses evaluated. The NOAEL for maternal and developmental toxicity of sodium azide in rats was therefore considered to be 5 mg/kg/day.

Recommendations

The main route of exposure to sodium azide at the workplace is by inhalation as a fine powder. Critical systemic endpoints are the direct vasodilatory effect and effects on the central nervous system, related to the cytotoxic effects of sodium azide and/or metabolites.

Acute effects

Quantitative data on human occupational exposure to sodium azide are scarce. The typical symptoms reported by workers (headache, vertigo, nausea, fatigue, palpitation of the heart, faintness) generally regarded as secondary to hypotension. The available data on chronic occupational inhalation exposure suggest that some of these symptoms may be caused by the direct vasodilatory or CNS effects of sodium azide as they appeared at lower levels of exposure that caused hypotension. On the other hand, hypotensive episodes verified by blood pressure monitoring occurred without subjective symptoms.

In the study of Trout et al., (1996) headache occurred more often than hypotensive episodes, verified by blood pressure monitoring and at lower air concentration levels, that induced hypotension: 4/11 workers reported mild headaches, while blood pressure monitoring revealed only one case of hypotensive episode occurring during the examination period in an otherwise asymptomatic worker with personal breathing zone (PBZ) air sample result of 1.7 mg/m^3 sodium azide. Two of the non-hypotensive workers with headache, were exposed to less than 0.23 mg/m^3 sodium azide according to PBZ air sample results and for a third worker with headache 3 consecutive PBZ air sample results measured within 3 hours were: trace, 0.31 and 0.43 mg/m^3, respectively.

Similarly, at the starting phase of the Rippen et al. (1996) study, when up to 7.5 mg/m^3 sodium azide concentrations were measured, 12/65 cases of headache were reported, and no hypotension. With the gradual decrease of the average exposure level to less than 0.5 mg/m^3, during the next 9 months the number of headaches decreased gradually to 1/65, while the occurrence of "blood pressure change" varied between 0 - 3/65 throughout the examination period. At the end of the study, when the lowest average air sodium azide concentration of 0.5 mg /m^3 was measured, 2 cases of "blood pressure changes" were observed among 65 workers.

In the study of Miljours and Brown (2003) a surprisingly high frequency of headache was reported: both among the 42 unexposed controls (34 %) and among the 41 workers (85 %) exposed to a relatively low sodium azide concentration (range: 0 to 0.93 mg/m^3), compared to the other studies. Hypotension was not reported at a mean exposure level of 0.23 mg /m^3.

From the available occupational exposure studies no NOAEL or LOAEL can be derived for headache. From the Miljours and Brown (2003) study it is also obvious that headache is not specific symptom for sodium azide exposure, as it occurred in 41 % of the unexposed controls. (No control groups were in other studies.)

From the available data (Rippen et al., 1996) the LOAEL for the occurrence of hypotensive episodes can be estimated as 0.5 mg /m^3.

Local effects

In the study of Trout et al. (1996) no irritation symptoms were reported among the 11 workers exposed up to 1.7 mg/m^3 sodium azide concentration.

In the Rippen et al. (1966) study eye or throat irritation symptoms occurred occasionally

(0 -5/65 cases) during the 9 months follow up and do not seem to be in close connection with the sodium azide air concentrations measured. At the end of the study (average air sodium azide at 0.5 mg/m^3) only 1 case of eye irritation was recorded among the 65 workers.

The Miljours and Braun (2003) study is not in line with the previous two studies, reporting "red or irritated" eyes during the past 5 workdays in 85 % of the 41 workers, but also in 34 % of the 42 controls at a mean exposure level of 0.23 mg/m^3, which makes the evaluation of these data difficult.

Repeated exposure

Regarding the effects of repeated sodium azide occupational exposure the following data are available:

In the Rippen et al. (1996) study the cross-shift changes of the mean arterial blood pressure were not significant, even at the beginning of the study (-3.8 mmHg), when the sodium azide exposure level was up to 7.5 mg/m^3. However, with the decrease of the exposure level in the following months to 0.5 mg/m^3, the cross shift change decreased significantly (-1.5 mmHg), compared to the earlier change. Also the group of 6 workers with personal breathing sample results above 0.3 mg/m^3 sodium azide had lower mean pre-exposure blood pressure than the other 6 workers with results less than 0.3 mg/m^3. This was attributed to their prior exposure at their activity area and individual work practices.

In the Miljours and Brown (2003) study the mean systolic blood pressure of the workers exposed to sodium azide for 5-30 years often at a level above 0.3 mg/m^3, was significantly lower than that of the controls (125 versus 131 mmHg).

From the above data, in case of repeated occupational sodium azide exposure the LOAEL for slightly lower mean blood pressure at a group level can be estimated around 0.3 mg/m^3.

In addition to the usual symptoms mentioned above, Miljours and Brown (2003) reported the tremor of the hands significantly more frequent in the sodium azide exposed workers at the beginning of the study (15 % versus 0 in the controls) and at the end of the third year, but not in the second year. It is also noteworthy, that this is the only study reporting tremor, despite tremor being an objective symptom easily detectable both by the observers and by the affected persons. The results of psychological and neuropsychological tests revealed impairments of mood, compared to the unexposed controls.

Other effects

Mutagenicity as observed in bacteria is not relevant for mammals, because of the specific metabolism of sodium azide in bacteria. Sodium azide was not significantly mutagenic in *Drosophila melanogaster* and did not or only slightly increased sex-linked recessive lethality. Positive effects were observed in a dominant lethal test in the housefly. No studies on mammals are available to adequately assess germ cell effects (Greim, 2003).

At concentrations of 5 and 10 mg/kg sodium azide there was no evidence of carcinogenicity in rats during a 2-year study.

The reproductive toxicity of this substance cannot be adequately assessed.

Developmental toxicity: the NOAEL for maternal and fetal toxic effects of sodium azide was found to be 5 mg/kg/day in rats treated on gestation days 6-19 by gavage; teratogenic effects were not observed at any of the doses administered, including a dose with severe maternal and fetal toxicity (Faqi et al., 2008).

Recommended OELs for sodium azide

Based on the available occupational inhalation data and the best possible estimation of LOAEL of 0.3 mg/m^3 for mean blood pressure decrease observed in workers at a group level, and a LOAEL of 0.5 mg/m^3 for the occurrence of acute hypotensive episodes, an 8-hour TWA of 0.1 mg/m^3 is recommended to prevent hypotension and the onset of acute symptoms.

The proposed OEL will also protect against the irritating effects of hydrazoic acid that may be present in the workplace air where sodium azide is handled.

The available dermal toxicity data are contradictory and are not sufficient to assign a "skin notation".

At the level recommended, no measurement difficulties are foreseen (HSE, 2000).

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Annex 1: Acute animal toxicity and irritation data for Sodium azide

Reference	*Route*	*Species (n)*	*Dose*	*LD_{min} mg/kg*	*LD_{50} mg/kg*	*LD_{100} mg/kg*
Graham (1949) cit. HSE (2000).	oral	mice			27	
Bassendowska and Kowalski, (1961)	subcutan	rats (20)	15-72 mg/kg in water	44.5	45.1	47.2
		mice (25)		20.4	23.06	49.0
	intratrach.	rats (12)	0.36-0.41ml water solution	46.0	47.5	49.0
	dermal irritation test	rabbits (2)	4 places (2 scarified), 10 mg/place, covered, + 20 mg into the conjuct. sac (summ: 60 mg)	death after 10 hours (no irritation)		
		rabbits (3)	rabbit 1: 20 mg into the conjuctival sac rabbit 2: 40 mg on the skin (13 mg/kg) rabbit 3: 60 mg on the skin (20 mg/kg?) for 24 hours	rabbit 1: survived 24 hours – no irritation rabbit 2: survived 24 hours – "local reaction" rabbit 3: death after 6 hours – no irritation „... lethal dose for rabbit was 18-21 mg/kg"		
Bassendowska et al., (1965)	skin	rats (20)				60
		Rabbits (?)	quoted from Bassendowska et al. (1961)			20
Potocar (1985)	skin irritation test	rabbits (6) (2-4 kg bw)	4x500 mg/animal on 4 3x3 cm gauze pads (2 occlusive, 2 semi-occlusive) 2 patches for 1 hour, 2 for 4 hours (estimated individual doses 500-1000 mg/kg, depending on the weight of the animal)	Evaluation: 1,24,48,72 hr, 7 days after removal of the patch No irritation after 1 h, corrosion after 4 h exposure 3 of 6 animals died – no further data on the time of the deaths		

Annex 2: Occupational inhalation exposure studies for Sodium azide

Reference	*subjects*	*Previous exposure and complaints*	*Study*	
			exposure measured	*medical observations*
Trout et al. 1996	**10 production operators + 1 maintenance worker** in a highly automated sodium azide production factory Age: 27-42 (mean 33) y.	Max. 3 years of exposure No measurement data. **Anamnestic complaints** in the **previous 6 months**: 10/11 had headaches, 9/11 had palpitations, 9/11 had „low" BP at least once.	**10 area** samples: **NaN_3: ND-0.69 mg/m³** **HN_3: ND-0.1 ppm** **25** Personal Breathing Samples: **- 9** samples in blend & pack area: → → **Tr – 1.7 mg/m³** (6 were > 0.3 mg/m³) **- 16** samples in other areas: → → → → **ND – 0.23 mg/m³**	Ambulatory Blood Pressure Monitoring → **1 hypotension: with PBZ 1.7 mg/m³** **2 mild headaches: (1 with PBZ: trace, 0.31, 0.4 mg/m³)** → **2 mild headaches**
Rippen et al. 1996	**65 workers** sodium azide production factory	air: NaN_3: **0.2-5.87 mg/m³** Main health complaints: pounding headaches, rapid pulse, perception of lower blood pressure	Area sampling.: **NaN_3: 1- 7.5 mg/m³** **HN_3: 0.45-2.81 ppm** **12** Personal Breathing Samples (15 minutes): **Group 1**: 6 samples: **0.36 – 1.49 mg/m³** **Group 2**: 6 samples: **0.01 - 0.15 mg/m³** **Follow up for 9 months**: exposure gradually decreased **At month 9:** area sampling: **0.5 mg/m³**	**12/65 headaches, 0-3/65 BP changes, no irritation** Blood pressure surveillance system: **No significant cross-shift changes in blood pressure** No significant difference between pre- and post-exposure BP, in any groups, but: **pre-exposure BP was significantly lower in Group 1**. („may be related to prior exposure relating to activity, work area and individual practices") **1/65 headache, 2/65 BP changes**

Reference	*subjects*	*Previous exposure and complaints*	*Study*	
			exposure measured	*medical observations*
Miljours and Braun 2003	**41 workers and 42 unexposed**	**5 – 30 years** "often above the limit value of **0.3 mg/m³** "	Personal Breathing Samples **NaN_3: 0.0 - 0.93 mg/m³** (mean: 0.23)	**Exposed** **Unexposed** **Systolic BP mmHg:** 125 131 **Acute symptoms** (past 5 days) **%** Headache 85 34 Red eyes 85 41 **Chronic symptoms** Palpitation 12 0 Trembling of the hand 15 0 In 2nd year no chronic symptom. In the 3rd year only palpitation, red eyes and trembling is significant. Number of affected decreased.