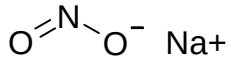
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	7632-00-0
Chemical Name	Sodium nitrite
Structural Formula	 $NaNO_2$

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Sodium nitrite has been reviewed by a number of international organizations: JECFA (Joint FAO/WHO Expert Committee on Food Additives); National Academy of Sciences (NAS); US National Institute of Environmental Health Sciences (NIEHS); National Institute of Public Health and the Environmental Hygiene, Netherlands; US National Toxicology Program (NTP); and California EPA (CAL/EPA).

Nitrite in blood is highly reactive with haemoglobin and causes methaemoglobinemia. Ferrous iron associated with haemoglobin is oxidized by nitrite to ferric iron, leading to the formation of methaemoglobin. Humans are considered to be more sensitive than rats in this respect.

The primary acute effect of sodium nitrite in rats and mice is methaemoglobinemia. Methaemoglobin concentrations in SD rats increased from 45% to 80% over 1 hour after an oral dose of sodium nitrite at 150 mg/kg bw and they returned to normal levels within 24 hours in surviving rats.

LD_{50} values by gavage are 214 mg/kg bw (males) and 216 mg/kg bw (females) in mice. In an acute inhalation study (which could not be validated) methaemoglobin levels in female rats were significantly increased after 4 hours exposure to 10 mg/m^3 sodium nitrite. The increase was judged not to be haematologically significant. No significant increase was observed in exposed males. There were no toxicologically significant effects on animals maintained for 14 days post exposure. No information on acute dermal toxicity is available.

Based on the available information, sodium nitrite is a moderate eye irritant, but is non-irritant to skin in rabbits. No studies are available investigating the sensitising potential of sodium nitrite in animals. No cases of sensitisation have been reported in humans.

In a repeated dose toxicity study [NTP] male and female F344/N rats were exposed to 0, 375, 750, 1500, 3000 or 5000 ppm sodium nitrite (equivalent to average daily doses of approximately 0, 30, 55, 115, 200, or 310 mg/kg bw/day in males and 0, 40, 80, 130, 225, or 345 mg/kg bw/day in females) in drinking water for 14 weeks. Methaemoglobin levels were significantly elevated in all treated groups compared to the controls by the end of the treatment period. For males, mean methaemoglobin levels after 14 weeks were 0.03±0.01, 0.08±0.01, 0.12±0.02, 0.25±0.07, 0.71±0.20 and 3.38±0.80 g/dL at doses of 0, 30, 55, 115, 200, and 310 mg/kg bw/day. For females, mean methaemoglobin levels after 14 weeks were 0.06±0.02, 0.14±0.02, 0.16±0.02, 0.48±0.05, 0.99±0.20 and 2.27±0.54 g/dL at doses of 0, 40, 80, 130, 225 and 345 mg/kg bw/day. The NOAELs were not determined (increased methaemoglobinaemia). The LOAELs for other endpoints were 115 mg/kg bw/day (decreased sperm motility) in males and 225 mg/kg bw/day (increased relative weight of the kidney and spleen) in females .

In a second 14-week repeated dose toxicity study [NTP] male and female B6C3F1 mice were exposed to 0, 375, 750,

1500, 3000 or 5000 ppm sodium nitrite (equivalent to average daily doses of approximately 0, 90, 190, 345, 750, or 990 mg/kg bw/day in males and 0, 120, 240, 445, 840, or 1230 mg/kg bw/day in females) in drinking water. Methaemoglobin levels were not reported however there were no clinical signs of toxicity. The LOAELs were 750 mg/kg bw/day (extramedullary haematopoiesis in the spleen, degeneration of the testis) in males and 445 mg/kg bw/day (extramedullary hematopoiesis in the spleen) in females.

In a two-year chronic toxicity/carcinogenicity study [NTP] male and female F344/N rats were exposed to 0, 750, 1500 or 3000 ppm sodium nitrite (equivalent to average daily doses of approximately 0, 35, 70 or 130 mg/kg bw/day in males and 0, 40, 80 or 150 mg/kg bw/day in females) in drinking water. There were no clinical findings related to exposure. Methaemoglobin levels were measured at two weeks and three months. At both 2 weeks and three months, methaemoglobin levels were high at night when the rats were actively feeding and drinking and low during the day when the rats were less active. Methaemoglobin levels tended to increase with increasing dosage.

In a second two-year study [NTP] male and female B6C3F1 mice were exposed to 0, 750, 1500 or 3000 ppm sodium nitrite (equivalent to average daily doses of approximately 0, 60, 120 or 220 mg/kg bw/day for males and 0, 45, 90 or 165 mg/kg bw/day for females) in drinking water. There were no clinical findings related to exposure. At 12 months, no significant increase in methaemoglobin level was observed in either sex at any dose.

Based on the two-year studies, the NOAELs for rats were 130 mg/kg bw/day in males and 150 mg/kg bw/day in females. For mice the NOAELs were 220 mg/kg bw/day in males and 165 mg/kg bw/day in females

Sodium nitrite is a direct-acting, base-pair substitution mutagen in organisms ranging from bacteria to mammalian cells *in vitro*. This substance induced chromosomal aberrations in mammalian cells *in vitro*. There is evidence of potential *in vivo* genotoxicity. The substance tested positive in a micronucleus test (peripheral blood) when mice were dosed by gavage at 10 to 20 mg/kg bw (4 times at 24 hrs intervals) but was negative in a second study where mice were dosed via drinking water at dosed up to 900 mg/kg bw/day (females) for 14 weeks. In a chromosomal aberration test, pregnant rats were dosed with 210 mg/kg bw/day for 13 days. Positive results for the induction of chromosomal aberrations in bone marrow of the parents and liver cells of embryos were reported.

In a two-year chronic toxicity/carcinogenicity study [NTP] male and female F344/N rats were exposed to 0, 750, 1500 or 3000 ppm sodium nitrite (equivalent to average daily doses of approximately 0, 35, 70 or 130 mg/kg bw/day for males and 0, 40, 80 or 150 mg/kg bw/day for females) in drinking water. The incidences of hyperplasia of the forestomach epithelium in high dose males (44/50) and females (40/50) were significantly greater than those in the control groups (12/50 males, 8/50 females). The incidence of fibroadenoma of the mammary gland was significantly increased in 80 mg/kg bw/day females, and the incidences of multiple fibroadenoma were increased in 40 and 80 mg/kg bw/day females; however these neoplasms occur with a high background incidence and no increase was seen in the high dose group. The incidences of mononuclear cell leukemia were significantly decreased in 70 and 130 mg/kg bw/day males (7/50 and 3/50, respectively) and 80 and 150 mg/kg bw/day females (1/50 and 1/50, respectively) compared with controls (17/50 males, 15/50 females). Under the conditions of this study there is no evidence of carcinogenic activity of sodium nitrite in F344/N rats at approximate doses of up to 130 mg/kg bw/day in males and 150 mg/kg bw/day in females over a two year period.

In another NTP study male and female B6C3F1 mice were exposed to 0, 750, 1500 or 3000 ppm sodium nitrite (equivalent to average daily doses of approximately 0, 60, 120 or 220 mg/kg bw/day for males and 0, 45, 90 or 165 mg/kg bw/day for females) in drinking water for two years. The incidences of squamous cell papilloma or carcinoma (combined) in the forestomach of female mice occurred with a positive trend (1/50, 0/50, 1/50 and 5/50 at doses of 0, 45, 90 or 165 mg/kg bw/day, respectively). The incidence of hyperplasia of the glandular stomach epithelium was significantly greater in 220 mg/kg bw/day males (10/50) than in the controls (0/50). Under the conditions of this study there is no evidence of carcinogenic activity of sodium nitrite in male B6C3F1 mice at doses up to approximately 220 mg/kg bw/day over a two year period. There is equivocal evidence of carcinogenic activity in female mice, based on the positive trend of squamous cell papilloma or carcinoma (combined) in the forestomach.

Various other carcinogenicity studies in rats were negative. Moreover, some even showed a reduction in tumor risk (e.g. lymphoma or leukemia). WHO concluded that there was no evidence of carcinogenic activity of sodium nitrite

in rats and mice based on the findings of NTP carcinogenicity studies.

There is evidence for transfer of sodium nitrite to fetuses in rats and mice. Reproductive success in the F1 generation was not affected. Increase in mortality of pre- and postnatal offspring and decrease in body weight of preweaning pups were observed in rat dams given a diet containing sodium nitrite at 0.0125% (10.75 mg/kg bw/day), 0.025% (21.5 mg/kg bw/day) and 0.05% (43 mg/kg bw/day), and the NOAEL is considered to be 10.75 mg/kg bw/day. Reproductive toxicity by continuous breeding in the mice was conducted with drinking water at doses of 125, 260 and 425 mg/kg bw/day, and no adverse effect on reproductive performance or necropsy endpoint were observed. The NOAEL is estimated to be 425 mg/kg bw/day. Sodium nitrite caused maternal anemia and the incidence of abortion and fetal mortality increased when administered to pregnant guinea pigs in drinking water and LOAEL is considered to be at 60 mg/kg bw/day.

From the weight of evidence, sodium nitrite appears to affect erythropoiesis, hematological parameters and brain development resulting in mortality and poor growth of offspring.

In humans, sodium nitrite causes smooth muscle relaxation, methaemoglobinemia, and cyanosis. Infants are particularly sensitive. A large proportion of haemoglobin in infants is in the foetal haemoglobin form, which is more readily oxidised to methaemoglobin than adult haemoglobin. Further, reduced nicotinamide-adenine dinucleotide (NADH)-dependent methaemoglobin reductase, the enzyme responsible for reduction of methaemoglobin back to normal haemoglobin, has only about half the activity present in adults.

Environment

Sodium nitrite is is in the form of white or slightly yellow hygroscopic granules, rod or powder, which is very soluble in water (820 g/L at 20 °C). Melting point, boiling point, vapour pressure and partition coefficient are 271 °C, >320 °C (decomposes), 9.9E-17 hPa (25°C) and log Kow = -3.7, respectively. Fugacity model Mackay level III calculations suggest that the substance will distribute mainly to soil if released to the air or soil compartments separately or to all three compartments simultaneously and almost exclusively to water if released to the water compartment. The estimated value of the Henry's law constant is 2.06E-07 atm.m^3/mole. This substance dissociates immediately into sodium and nitrite ions in water. The nitrite ion is a component of the nitrogen cycle. In the environment, bacteria of the genus Nitrobacter oxidise nitrites to nitrates. Nitrates are reduced to nitrogen by anaerobic bacteria present in soil and sediment. The estimated BCF is 3.2 and hence bioaccumulation is not significant. Indirect photo-oxidation by hydroxy radicals is predicted to occur with a half-life estimated at 82.3 days.

The LC_{50} values for the acute toxicity of sodium nitrite to fish reported in the literature vary widely between the species tested; LC_{50} (96h) = 0.54 mg $NaNO_2$/L for *Oncorhynchus mykiss*; LC_{50} (96h) = 35 mg $NaNO_2$/L for *Ictalurus punctatus*; LC_{50} (96h) = 691.0 mg $NaNO_2$/L for *Micropterus salmoides*; and LC_{50} (96h) = 1010.4 mg $NaNO_2$/L for *Anguilla japonica*, for example. This difference has been attributed to the ability of certain species, such as eels, bass and sunfish to prevent nitrite from crossing the gill membrane and entering the blood, whilst other species such as rainbow trout concentrate nitrite in their blood. The range of toxicity values reported for some species of fish varies widely and is believed to be dependant on the quality of the water used in the test with pH, chloride and calcium ion concentration all having an influence. In particular, chloride ion concentration has been shown to be important, with increasing concentrations leading to a decrease in the toxicity of nitrite. As with fish, there is variation in toxicity between invertebrate species. Sodium nitrite is toxic to invertebrates such as *Cherax quadricarinatus* (LC_{50} (96h) = 4.93 mg $NaNO_2$/L and *Thamnocephalus platyurus* (LC_{50} (24h) = 3.9 mg $NaNO_2$/L), whereas other species, such as *Procambarus clarkii* (LC_{50} (96h) = 18.7 mg $NaNO_2$/L) and *Penaeus paulensis* are much less sensitive (LC_{50} (96h) = 539.2 mg $NaNO_2$/L). The presence of chloride ions has been found to mitigate nitrite toxicity in some species. There is a data gap because no study performed in accordance with a standard guideline method was available for acute toxicity to algae. The CO_2-fixing activity of blue-green algae was reported to be much more sensitive to nitrite than that of other algae, including green algae (greater than 90% inhibition compared with less than 19% at a dose of 69 mg/L-$NaNO_2$, respectively) The IC_{50} ($^{14}CO_2$ uptake) by one species of blue-green algae was calculated to be 6.9 mg/L-$NaNO_2$.

No data is available for chronic toxicity of sodium nitrite in fish or algae. In invertebrates, an 80-day NOEC of 9.86 mg $NaNO_2$/L for *Penaeus monodon* has been reported.

For other aquatic organisms, the EC_{50} (48h, deformation) and LC_{50} (48h) for the protozoa *Spirostomum ambiguum* were 421 and 533 mg $NaNO_2$/L, respectively; for the microalgae *Tetraselmis chuii* the EC_{50} (96h, mobility) and NOEC (96h, mobility) were 7886 and 3740 mg $NaNO_2$/L, respectively.

Exposure

Total production of sodium nitrite in Japan was 10,000 - 50,000 t/year in 2001. Information on the worldwide production volume of sodium nitrite is not available.

This substance is used in closed systems, for non dispersive use, and also for wide dispersive use. Workers are recommended to wear protective gear such as a mask, rubber gloves and goggles to prevent exposure. There are no available official recommendations or regulations for occupational exposure limits to this substance. This substance is widely used in various industries including agricultural, basic chemicals, chemical industry, and others. The use in synthesis includes the use as raw material for the production of caprolactam and others. This substance is used widely as food/foodstuff additive, corrosion inhibitor, and so forth.

The nitrite ion is ubiquitous in the environment, where it forms part of the nitrogen cycle. The source of nitrogen is natural or anthropogenic. Fertilizers are considered to be the main anthropogenic source of nitrogen, although anthropogenic nitrogen oxide and dioxide present in the atmosphere from combustion processes are also sources of nitrite and nitrate in soils and surface waters, delivered via acid rain. Naturally occurring nitrogen oxide and dioxide in the atmosphere are also possible sources of nitrite. It should be noted that although the nitrite ion (NO_2^-) may cause a concern when assessing the potential eutrophication hazard including drinking water quality in certain regions, the use of this substance ($NaNO_2$) as a fertilizer has not been reported. Therefore this substance has a potential of eutrophication, but its influence is lower than that of the fertilizers.

The most common source of exposure of anthropogenic sodium nitrite to consumers is from its use in cured meat products. Exposure to nitrite also occurs from vegetables and drinking water. Nitrite can be formed in the body through reduction of nitrate by enteric bacteria and mammalian nitrate reductase. The Joint FAO/WHO Expert Committee on Food Additives established an acceptable daily nitrite intake of 0 to 0.07 mg/kg bw/day. Various countries have set limits for nitrite through water quality regulations.

RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

The chemical possesses properties indicating a hazard to human health (acute toxicity, irritation, repeated toxicity, mutagenicity, and reproductive toxicity) and the environment (acute toxicity). Given the wide dispersive use of this substance, member countries are invited to perform an exposure assessment, and if necessary a risk assessment for these uses. It is acknowledged that some uses (e.g. as a food additive) as well as the presence in drinking water are already regulated in many member countries. It should be noted that there is no standard acute algae study available, however further study is not warranted. It is recommended that the information on possible total exposure from regulated and non-regulated use be shared between regulatory agencies.