UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

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DATE: September 18, 2007

SUBJECT: **Human Studies Review Board:** Weight of Evidence Discussion for Sodium azide (NaN_3)
DP Barcode D343907
PC Code: 107701

FROM: Nancy McCarroll
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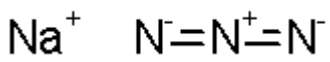
This document describes the scientific support for deriving a point of departure (PoD) for sodium azide (NaN_3) using data from an experimental oral therapeutic dose human study Master Record Identification Number (MRID No. 47221401**)**. The PoD is supported by data from reports of accidental human ingestion as well as by animal toxicity studies (MRID Nos.46245010 and 46642301). This PoD is applicable for use in acute and chronic dietary and non-dietary exposure risk assessments.

1. **Background and Introduction:**

Sodium azide (NaN_3) has been used for many years as a laboratory reagent and as a raw material for production of azide-containing compounds. It has been used as a pharmaceutical intermediate and as a blood, laboratory reagent and/or biological fluids preservative. It has also been used as a gas generant in airbags. Airbag propellants

containing NaN_3 were very common in early inflator designs. However, propellants containing NaN_3 were phased out during the 1990s in pursuit of more efficient, less expensive and less toxic alternatives. In the past, NaN_3 was used as a pharmaceutical to treat high blood pressure and as an anti-neoplastic agent. The pharmaceutical and laboratory use of NaN_3 accounts for the human toxicity data that are presented in this document. American Pacific Corporation (AmPac) is seeking registration of NaN_3 as a replacement for methyl bromide and is requesting very limited uses. These limited uses consist of: commercial production of ornamental cut flowers and pre-plant application via drip tape irrigation on beds under plastic mulch; sod farms with pre-plant applications to soil with tarping after application; and golf course turf area renovation with pre-plant application and immediate tarping. Based on the available information, it is assumed that there will be possible oral, dermal and inhalation exposures.



Chemical Structure of Sodium Azide

Reliable animal toxicity studies are available; however, to derive an appropriate PoD for assessing human health risk, human studies are preferable because data will be presented showing that humans are more sensitive to the toxic action of NaN_3 than animals. Additionally, human data from reports of NaN_3 accidental exposure also show that humans are more sensitive to NaN_3 than animals. In accordance with the human studies rule, the Agency is requesting the Human Studies Review Board (HSRB) to review the ethical and scientific conduct and design of a single study presenting the findings of the therapeutic effects of NaN_3 as an antihypertensive agent.

2. Hazard Characterizations and Database Summary

NaN_3 acts as a metabolic inhibitor that interferes with oxidative enzymes. Azide anions prevent the cells of the body from using oxygen, inhibiting the function of cytochrome oxidase by binding irreversibly to the heme cofactor in a process similar to that of carbon monoxide. When this happens, the cells die. NaN_3 is converted to nitric oxide (NO), and it is likely that this conversion accounts for its toxicity (Smith et al., 1991). NaN_3 is more harmful to the heart and the brain than to other organs, because the heart and the brain require a constant supply of oxygen.

A. Animal Data

Summarized results from relevant animal studies are presented in Table 1. As shown, NaN_3 is acutely toxic, causing hypotension in hypertensive rats after intravenous exposure (0.6-0.7 mg/kg), neurotoxic in rats after subchronic or chronic oral exposure (≥5 mg/kg/day) and in dogs after oral subchronic exposure (1 mg/kg). It is not carcinogenic, but produces toxic effects in rat fetuses at doses that are maternally toxic (MRIDs 46642301, 00109268/46642301, 46245003, 46245004, 46836601, 47221401).

Table 1. Summary of Animal Studies Performed on Sodium Azide

Study Type	Doses (mg/kg/day)	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Comment	Source/ Mrid No.
Acute Intravenous (rat)	0.1 mg/kg		0.67 to 0.6[a]	Lowered blood pressure in rats with induced hyper-tension; no effect on normotensive rats	Effects lasted 30-45 minutes	Black et al., 1954 MRID 47221401
26 week oral gel capsule (dog)	0, 1, 3, 10	1	3	Hind leg weakness		Hoberman et al.,1981 MRIDS 00109268 46642301
14-day oral gavage (rat)	0, 5, 10, 20, 40, 80	10	20	Lethargy, inactivity, death	No neurotoxicity; lethality at higher doses	NTP 1991 MRID 46245003
13-week oral gavage (rat)	0, 1.25, 2.5, 5, 10, 20	10	20	Death and brain lesions in both sexes		NTP 1991 MRID 46245003
2 year oral gavage (rat)	0, 5, 10	5	10	↓ Survival associ-ated with high inci-dence of brain necrosis and pulmo-nary congestion		NTP 1991 MRID 46245003
Developmental Toxicity (Syrian golden hamsters) subcutaneous	0, 1.1-6 x 10^{-2} mmol/kg/hr ≈0.7-3.9 mg/kg/hr to pregnant dams on GD 7 & 8	Mater: 3.5 mg/kg/hr Develop: 3.5 mg/kg/hr	Mater: 3.9 mg/kg/hr Develop: 3.9 mg/kg/hr	Mater: Dyspnea, hypo-thermia & ataxia Develop:15%↓ in fetuses/litter and an ↑ fetal resorptions and encephaloceles	Unacceptable, but shows qualitatively toxic effects on the fetus at maternally toxic dose.	Sana et al., 1990 MRID 46245004
Developmental Toxicity oral gavage (rat)	0, 1, 5 to pregnant dams on GD 6 & 19	Mater: 5 Develop: 5	Mater: 10 Develop: 10	Mater:↑ mortality, ↓ bodyweight gain & food consumption & other toxic signs (↓ activity, impaired limb function, prostration, loss of or impairment of righting reflex, lacrimation, abnormal breathing). Develop:↓ fetal body weight in fetuses	Toxic effects on the fetus occur at maternally toxic dose. Neurotoxic signs at the LOAEL	Faqui, 2006 MRID 46836601

[a] Based on rat body weights of 150-180 g.

B. Mutagenicity Data

NaN_3 is a powerful mutagen in bacterial systems. It is weakly mutagenic, causing, forward gene mutations in cultured mammalian cells (L5178Y mouse lymphoma cells and Chinese hamster ovary cells) but not in Chinese hamster V79 lung fibroblasts and is not clastogenic in human lymphocytes. *In vivo,* there is evidence of dominant lethal mutations and sterility in domestic flies but not dominant lethal mutations in rat germinal cells in *Drosophilia* or structural or numerical chromosomes in rat somatic cells. The absence of a mutagenic effect in these latter *in vivo* test systems is consistent with the lack of evidence of carcinogenic activity in the 2-year NTP bioassay conducted with F344/N rats receiving oral gavage dose of NaN_3. NaN_3 mutagenicity is mediated through a metabolic process that is not available to mammals. Since the mutagenic metabolite, azidoalanine is not synthesized by animals; there are no mutagenic concerns for humans (MRIDs 46245003, 05-09).

B. Human Data

1. Experimental Oral Therapeutic Dosing

MRID 47221401. Comparison of Hypotensive Action of Sodium Azide in Normotensive and Hypertensive Patients. Black *et al.*, 1954:

In the study of **Black et al (1954)**, experimental oral therapeutic doses of 0.65 to 1.3 mg (≈0.01 to 0.02 mg/kg)[1] NaN_3 were studied. For the acute phase, 30-35 patients were studied. For the chronic phase, subjects were divided into groups of 30 hypertensive patients (documented cases of elevated blood pressure, recorded "from 12 months to as long as 10 years") and 9 normotensive individuals (9 controls made up of normal healthy students and laboratory personnel as well as patients with diverse types of cancer) who received NaN_3 doses over periods that ranged from 5 days to more than 2 years. In 13 patients (initial systolic pressures were ≥190 mm Hg), acute doses of 0.65 to 1.3 mg caused an average drop of 43 mm Hg (range –30 to –65 mm Hg) in blood pressure. A marked decrease in the blood pressure of some hypertensive patients was reported as early as 45 to 60 seconds after treatment with 1.3 mg (0.02 mg/kg, based on a 70-kg adult). The blood pressure reduction was more pronounced in one of these patients after 8 days of treatment with 1.3 mg/3X/day for 8 days. By contrast, administration of a comparable dose 3 times per day to 9 normotensive individuals (total daily dose = 0.6 mg/kg, based on a 70-kg adult) for 10 days had no sustained effect on blood pressure. We assume that no effects were seen after 1 day of dosing.

In the chronic phase of testing, the 30 hypertensive patients, treated with 0.65 to 1.3 mg NaN_3 (at least 3X/day) for 10 days up to 2½ years, the following signs were shown: 5 cases showed minimal changes in blood pressure; 10 exhibited a significant fall but the diastolic pressure remained above 100 mm Hg; and 15 had persistent blood

[1] Doses of 0.65 or 1.3 mg were adjusted for a 70 kg male by ÷ the dose by 70 kg which = 0.01 or 0.02 mg/kg, respectively. Since the sex of these subjects was not reported, the more conservative estimate of body weight, 70 kg was used to adjust the doses to mg/kg.

pressure levels near normal and the 3 patients, who were checked for clinical signs, showed no evidence of damage to kidneys, heart, or liver and no changes in bowel habits or urinary function after 1 year. Twenty patients continued on treatment (for an unreported interval) developed an increased sensitivity to NaN_3, necessitating a daily dose reduction from 0.5 to 0.25 mg 3X/day. Whether this was a toxic effect other than a further lowering of the blood pressure was not made clear. Nevertheless, these data suggest that an acute total dose as low as 0.65 mg 3X/day (total daily dose = 1.95 mg or 0.03 mg/kg, based on a 70-kg adult) had a beneficial effect on patients with high blood pressure while a total dose of 1.3 mg 3X/day (total daily dose = 3.9 mg or 0.06 mg/kg, based on a 70-kg adult) had no adverse effects on normotensive individuals. Similarly, chronic doses as low as 0.25 mg 3X/day (total daily dose = 0.75 mg or 0.01 mg/kg, based on a 70-kg adult) produced beneficial effects on the blood pressure of hypertensive patients while doses of 0.01 to 0.02 mg/kg (3X/day) for periods up to 1 year had no adverse effects on kidneys, heart or liver on the basis of routine clinical studies in hypertensive patients.

Based on the above information, a NOAEL for NaN_3 in hypertensive individuals could not be established; however, a NOAEL of 0.06 mg/kg for normotensive individuals was determined.

2. Accidental Ingestion

MRID 46245010. Human Health Effects of Sodium azide
MRID 46642301. Sodium azide: Human and animal toxicity data.

Twelve articles on accidental ingestion or occupational exposure to NaN_3 are presented in these two MRIDs. In general, these studies indicated that death occurs at doses as low as 10 mg/kg (Judge and Ward, 1989, as cited in Chang and Lamm, 2003), while headache, restlessness, and polydipsis are seen at 2 mg/kg in the study of Burger, 1965 (as cited in Chang and Lamm, 2003). The most frequent observation at doses $\leq$1 mg/kg is hypotension (Table 2). Presented below are summaries of studies showing health effects at the lower end of the dose spectrum.

Edmonds and Bourne (1982) reported on the accidental ingestion of tea containing 40 mg NaN_3 by five laboratory workers. The three females, who ingested one cup of tea (40 mg NaN_3, $\approx$0.67 mg/kg for a 60 kg female), showed signs of dizziness, pounding heart and faintness; these symptoms "disappeared quickly and completely". The individual ingesting only one-half a cup (20 mg NaN_3, $\approx$0.34 mg/kg for a 60 kg female) felt "vaguely unwell" and was affected "to a lesser degree"; the symptoms were "short-lived". For the male patient ingesting 2 cups (80 mg NaN_3, $\approx$1.14 mg/kg for a 70 kg male), symptoms of myocardial ischemia were observed with an initial rapid recovery within a few hours.

Table 2. Summary of Representative Human Oral Studies with Sodium Azide

Exposure Scenario	Dose (mg)	Dose (mg/kg)	Effect	Source
Therapeutic	0.65-1.3 3X/day (5 days to 2 yrs)	0.01-0.02 [a]	Lowering of blood pressure in hypertensive patients (25/30 patients)	Black et al., 1954 MRID 47221401
	0.25 3x/day	0.004 [a]	Lowering of blood pressure in hypertensive patients (20 patients) with an increased sensitivity to NaN_3	
	1.3 1X	0.02 [a]	Lowering of blood pressure in "some" hypertensive patients within 45 to 60 seconds	
	0.65-1.3 3X/day (10 days to 2 yrs)	0.01-0.02 [a]	No adverse effects on subjects with normal blood pressure (9 subjects)	
Accidental ingestion	20 40 80	0.34 (1♀) [b] 0.67 (3♀) [b] 1.14 (1♀) [b]	Vaguely unwell to a lesser extent than 40 mg Dizziness, palpitation, chest pain, faintness Myocardial ischemia	Edmonds and Bourne, 1982
	60	1 (1♀) [c]	Nausea, altered consciousness with confusion, vomiting, diarrhea	Howard et al., 1989
	40	0.7 (1♀) [b]	Tachycardia, hyper ventilation, hypotension	Roberts et al., 1974
	50-60	0.7-.9 (2♀) [b]	Lost consciousness, urinary incontinence feeling hot, sweating, paleness, tachycardia,	Richardson et al., 1975
	150	2 [a]	Headache, restlessness, EKG changes, polydipsia	Burger, 1965
	700-800	10 -11 (1♀) [c]	Seizure, arrhythmia, chest pain, dyspnea, diarrhea, nausea, death	Judge and Ward, 1989

[a] Based on an adult male body weight of 70 mg/kg.
[b] Based on an adult body weight of 60 mg/kg, listed by the study author.
[c] Based on an adult female body weight of 52 mg/kg

Note: In cases where the sex was not reported, the more conservative estimate of adult body weight (70 mg/kg) was used.

Richardson et al. (1975) also reported the accidental ingestion of Isoton (diluent that contains 0.1% NaN_3 and is used for hematological measurements in Coulter Model S Counters) by a patient and a laboratory technician in a hospital laboratory. It was estimated that the patient ingested 50 to 60 mg (≈0.7 to 0.9 mg/kg for a 70 kg male); within 5 minutes, the patient collapsed, lost consciousness and showed urinary incontinence. After 10 minutes, the individual complained of feeling hot, nauseated, and had a severe headache; urinary incontinence and a drop in blood pressure (100/60 mm Hg) were also reported. After 1 hour, his blood pressure returned to normal (120/80 mm Hg) and only the headache continued until the next morning. The study authors stated, "When seen a week later he was well." A subsequent 1-week follow-up revealed no evidence of persistent toxic effects; and he was reported to be "well". Based on the presented information, we assume that 120/80 mm Hg was normal for this individual. However, the decrease in blood pressure was considered "questionable" by the sponsor's representative[2].

Using the criteria reported in the DER for MRID 46642301 and adopted by the National Institute of Health (NIH) for hypotension (i.e., "drop from baseline of 20 mm Hg in systolic blood pressure and of 10 mm Hg in diastolic blood pressure") and the assumption that 120/80 mm Hg was normal for this individual, we disagree with the above statement of the sponsor's representative that the drop in blood pressure was questionable hypotension.

For the second victim, the laboratory technician complained of headache, sweating, and faintness within 5 minutes; these symptoms "passed rapidly" and the estimated dosage was 5 to 10 mg NaN_3 (≈0.07 to 0.14 mg/kg for a 60 kg female).

Roberts et al. (1974) reported the accidental ingestion of 4% NaN_3 by a laboratory technician. In this incident, symptoms of tachycardia, hyperventilation and hypotension were observed with complete recovery within 24 hours. The investigators estimated that the ingestion of 1 mL of the 4% concentration (4000 µg/mL) "would provide a dose of 70 µg/kg for a 60-kg adult". However, our reviewers uncovered a calculation error: conversion of the 4% solution would actually yield 40,000 µg/mL not 4000 µg/mL, as stated by the study authors. Accordingly, the correct estimate of ingestion of 1 mL of the 4% NaN_3 solution should be 0.7 mg/kg for a 60-kg female adult. These authors also stated that the hypotensive dose of NaN_3 in the human is 0.2 to 4 µg/kg; the source of this information was not provided. Nevertheless, the corrected dose (700 µg/kg) is well in excess of these levels.

Howard et al., (1989) also report on accidental ingestion of an isotonic buffered saline solution containing 1.0 g/mL NaN_3. This incident involved two college students, one of whom ingested "three sips" and within 5 minutes experienced nausea and altered consciousness with confusion, followed by vomiting and diarrhea. This woman collapsed but her symptoms declined with time and she survived. Chang and Lamm

[2] Sodium azide: Critical Review of Human Health Effects Literature and Path Forward, dated April 30, 2007, American Pacific Corp. Presented at Health Effects Division (HED) of the Office of Pesticides (OPP) May 7, 2007.

(2003) estimated the dose consumed by this person to be 3-5 mg or 0.05- to 0.08 mg/kg (See MRID 46245010). However, Lawless et al (2003) estimated that 1 sip is equivalent to 20 mL for a human female; therefore, the volume consumed by this victim was ≈60 mL. Using this information, which was furnished by the sponsor's representative, our reviewers estimated that the dose of NaN_3 would be 60 mg or 1 mg/kg for a 60- kg female.

GENERAL DISCUSSION

Several issues need to be resolved from the data submitted by the sponsor. The first of these issues relates specifically to the adequacy of the human data and must be addressed before the analysis can continue.

Adequacy of the human data

The database for NaN_3 contains many human studies documenting the accidental or intentional (suicidal) ingestion as well as the therapeutic effects of NaN_3 (MRIDs 46245010, 46642301 and 47221401). These studies date from 1947 to 1996 and describe the outcome of exposure of individuals or several victims. None of these studies were ever intended for submission to the U.S. EPA for the determination of toxicological endpoints used in regulation; nevertheless, when viewed collectively, the findings provide compelling evidence of a dose response (i.e., as the dose increases, the severity of the effects increases). Additionally, in studies where victims are exposed to nonlethal doses, the finding of toxic effects on the cardiovascular system is consistently reproduced. This is not unexpected since NaN_3 has a long incidental history as a possible agent to treat hypertension dating back to the work of Keilin and Hartree, (1934 as cited by Black et al 1954) and Page and Olmsted (1951 as cited in Black et 1954). Hypertension, as described by the NIH, generally means:

- Systolic blood pressure is consistently over 140 (systolic is the "top" number of your blood pressure measurement, which represents the pressure generated when the heart beats)
- Diastolic blood pressure is consistently over 90 (diastolic is the "bottom" number of your blood pressure measurement, which represents the pressure in the vessels when the heart is at rest)

Either or both of these numbers may be too high

This incidental information prompted Black et al (1954) to conduct the investigational dosing study of NaN_3 in both normotensive and hypertensive patients. An animal component to this study was also conducted in hypertensive and normotensive rats. This study, which is over 50 years old, was not intended for submission to a regulatory agency such as EPA. Thus, the article contains very little background information on the patients. The patient population (sex not specified) consisted of normotensive individuals (9 controls made up of normal healthy students and laboratory

personnel as well as patients with diverse types of cancer) and 30 hypertensive patients (documented cases of elevated blood pressure, recorded "from 12 months to as long as 10 years").

The major scientific flaw in the study was acknowledged by the study authors: "In view of the small size of the present series of cases treated with sodium azide, it should be emphasized that its clinical evaluation must await considerable further investigation, especially in terms of the mode of administration and the possible use of other azide derivatives. The necessity remains to rule out all possible toxic effects of long continued administration of sodium azide before routine use in the treatment of hypertension is attempted." We agree with this assessment of Black et al. that the data are not sufficient to fully evaluate chronic effects of NaN_3 in either healthy humans or individuals suffering from hypertension. However, we believe that while the data are limited, they do have merit and may be used to support the human health risk assessment. Similarly, human studies from accidental ingestion or occupational exposure can be used to address the issues outlined below:

1. Sensitivity of humans versus animals to the toxic effects of NaN_3
2. Neurotoxicity of NaN_3

Sensitivity of humans versus animals to the toxic effects of NaN_3

As shown in Table 1, intravenous (i.v.) doses as low as 0.6 to 0.7 mg/kg/day caused a lowering of the blood pressure in hypertensive rats (just as in humans) while producing no effects in normal rats. In comparison, rat levels are ≈ 30 to 35 X higher that the oral dose (0.02 mg/kg) producing a reduction in the blood pressure of a hypertensive human subject within 45 to 60 seconds (Table 2). In dogs, the lowest dose inducing adverse effects (hind limb weakness seen just prior to study termination after 26 weeks of treatment) in the subchronic study is 3 mg/kg/day (MRID 46642301). This LOAEL (3 mg/kg) is ≈ 150 X higher and took a significantly longer period of exposure (26 weeks) to produce toxicity than the human dose of 0.02 mg/kg. Based on this comparative analysis, we conclude that the data support the observation that humans are more sensitive to NaN_3 than animals.

Neurotoxicty of NaN_3

In addition to cardiovascular effects, NaN_3 is also neurotoxic. As further shown in Table 1, the lowest NOAEL (1 mg/kg/day) from an acceptable dog study comes from the 26-week dog study in which neurotoxic effects (hind leg weakness) were found at the LOAEL of 3 mg/kg/day. Other evidence of neurotoxicity is seen in the 13-week oral gavage rat study (brain lesions) at the LOAEL of 20 mg/kg/day and in the 2-year rat study, manifested as brain necrosis, at the LOAEL of 10 mg/kg/day. Several points are of interest: first, the longer the exposure duration in rats, the more prevalent neurotoxicity becomes. For example, no neurotoxicity is observed in the 14-day rat study at levels up to lethality while a comparable dose in the 13-week study produced not only death but also brain lesions. Additionally, the dose required to induce neurotoxicity in the chronic study

(2 years) (10 mg/kg/day) is half of the dose required to induce neurotoxicity after 13 weeks. Second, these data suggest that there is a clearly enhanced sensitivity of canines versus rats to the neurotoxic action of NaN_3. This is indicated by the LOAELs of the 26-week dog study (3 mg/kg) versus the chronic rat study (10 mg/kg). Thus, 2 years of exposure were required to produce neurotoxicity in rats but still at a higher level than the neurotoxicity seen in dogs. Studies suggesting neurotoxicity in humans are summarized in Table 2. As shown, the limited information in the Howard et al study precludes a determination of whether the clinical sign of altered consciousness seen in the victim was a neurotoxic effect or a manifestation of cardiovascular effects. Evidence of neurotoxicity at this minimal level is doubtful since the lowest dose, showing obvious signs of neurotoxicity in humans, was found in the accidental ingestion study of Judge and Ward (1989). In this study, the victim had seizures prior to death resulting from ingestion of ≈10 mg/kg NaN_3. Seizures are sometimes seen in human azide poisonings and are a typical feature of azide poisonings in laboratory animals (Smith et al, 1991). It is of note that this dose (10 mg/kg) is at least 4 orders of magnitude higher than the lowest level causing hypotension (0.004 mg/kg) in sensitized hypertensive patients. It can be concluded, therefore, that neurotoxicity is not the most sensitive endpoint to establish safe regulatory doses.

C. Point of Departure

The Black et al. (1954) experimental oral therapeutic dosing study in human subjects and the accidental ingestion studies reported by Edmonds and Bourne (1982); Howard et al. (1989); Roberts et al. (1974) and Richardson et al. (1975) have been discussed in this document or the review of studies compiled in MRIDs 46245010, 46642301 and 47221401. These data provide the most useful information for establishing an acute and a chronic PoD for the risk assessment from exposure to NaN_3. We have acknowledged the shortcomings of the Black et al. study; nevertheless, we conclude that despite these limitations, the PoD would be much lower with the human data than with the animal data, and therefore, more protective.

Acute

Results complied from the four accounts of acute exposure via accidental ingestions published from 1975 to 1989 are summarized in Table 2. Although the various reports detail the events surrounding the accidental poisoning of only a single or a few victims, when taken collective, there is a remarkable consistency in the acute dose causing toxicity in a total of 9 adult females. Toxic effects generally included: hypotension, nausea, tachycardia, altered consciousness, and other clinical signs over a dose range of 0.7 to 1 mg/kg. This supports the observation that the lack of an effect on nine normal patients at the daily dose of 0.06 mg/kg (Black et al., 1954, MRID 47221401) constitutes the acute NOAEL for normal individuals. An uncertainty factor of 10X will be applied to account for potential individual variability (intraspecies) in the human population.

Chronic

As indicated in study evaluation of MRID 47221401 and shown in Table 2, the lowest reported health effect was a decrease in blood pressure (in hypertensive patients) at 0.004 mg/kg (owing to an increased sensitivity to NaN_3) while total daily doses of 0.04 to 0.06 mg/kg (for 10 days) had no effects on nine normal patients (Black et al., 1954). No additional data were provided for the normal subjects. Accordingly, the NOAEL for normal individuals is 0.06 mg/kg.

An uncertainty factor of 10X will be applied to account for individual variability (intraspecies) in the human population. Additional uncertainty factors may be applied to account for the use of a PoD based on an acute/subchronic NOAEL for the chronic exposure.

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