approximately 20 minutes to 1 hour (ATSDR 2006, RIVM 2000, WHO 1997). The thiocyanate is excreted by the kidney with an elimination half-life of about 3 days in healthy persons but 7-9 days in subjects with impaired renal function (Schulz et al. 1979). Orally administered cyanide and its metabolite thiocyanate were eliminated in the breast milk of lactating goats (Soto-Blanco and Gorniak 2003)[15]. Studies on the transfer of cyanide into breast milk of other mammals, including humans, were not found.

4.2 Acute toxicity

4.2.1 Oral toxicity

Health information for acute oral CN^- exposure comes from human poisoning incidents.

In humans ingesting 4.6-15 mg CN^-/kg as KCN, serious adverse effects were observed on the nervous system (brain lesions, Parkinsonian-like signs, decreased verbal fluency, reduced information processing, coma), respiratory system (hyperventilation), cardiovascular system (shallow pulse, enlarged heart, and inaudible heart sounds), gastrointestinal system (nausea and vomiting), renal system (albinuria), and musculoskeletal system (generalised muscular rigidity) (ATSDR 2006). Symptoms may be delayed for 2-4 hours if ingestion of cyanide occurs on a full stomach (HPA 2010). Based on case reports of intentional or accidental poisonings, ATSDR (2006) estimated the acute oral median lethal dose in humans to be 1.52 mg CN^-/kg. However they do not provide the details of how this figure was calculated.

Oral LD_{50} in rodents for CN^- released from Na, K or Ca cyanide salts are 4-22 mg CN/kg bw (Table 4.1). While the single-dose gavage LD_{50} of KCN was 10 mg/kg bw in rats (i.e. 4 mg CN^-/kg) in one study, no mortality was observed when a dose of 250 mg/kg bw (i.e. 99.9 mg CN^-/kg) was given in the diet for 90 days (Hayes 1967). The author ascribed this difference to the difference in dose rate (bolus vs. dietary exposure). At the daily low dietary dose, the liver is capable of detoxifying cyanide before it reaches the general circulation.

[15] Twenty-eight female goats were bred to one buck. At day of birth, dams were divided into 4 equal groups and dosed with 0, 1, 2, or 3 mg KCN/kg bw/d (0, 0.4, 0.8, 1.2 mg CN/kg bw/d), administered orally with tap water, for 3 months. Whole blood cyanide and plasma thiocyanate levels were measured in dams and kids on the 30th, 60th and 90th days of the experiment. Both thiocyanate and cyanide levels presented a dose and time-dependent increase in all dams. In kids, the thiocyanate levels were increased dose-dependently, with a peak on the 30th day. On the 30th day, concentrations of thiocyanate in kids were approximately 70-100% of that in dams. Concentrations of cyanide in treated kids were increased only on the 30th day, detectable but not quantifiable on the 60th and undetectable on the 90th day. On the 30th day, total cyanide levels in kids were approximately 30-40% of that in dams. No control animals had detectable levels of cyanide in blood (detection limit not reported).

Developmental effects (delayed ossification and 23% reduction in foetal weight) were observed in offspring of hamsters ingesting cassava at an equivalent dose of 1 mg CN^-/kg/d on gestational days 3-14 (Frakes et al 1986). Foetal effects occurred despite the absence of overt toxicity in dams at doses as high as 10.4 mg/kg/d. However, the presence of other chemicals such as scopoletin[16] in cassava confounds the results from this study.

Table 4.1: Oral LD_{50}s for soluble cyanide salts

Species	Cyanide salt	LD_{50} (mg CN/kg/d) [a]	Source
Rat	$Ca(CN)_2$	22	Smyth et al 1969, as cited in ATSDR 2006
	NaCN	8	
	NaCN	2.7 (starved) 3.0 (fed)	Ballantyne 1984, as cited in WHO 1997 & Gezondheidsraad 2002
	KCN	3.9 (starved) 3.0 (fed)	
Rabbit	NaCN	2.7 (fed)	Ballantyne 1984, as cited in WHO 1997 & Gezondheidsraad 2002
	KCN	2.3 (fed)	
Mouse	KCN	4.3 - 6.3	Ferguson 1962
	KCN	3.4	Ballantyne 1984, as cited in Gezondheidsraad 2002

[a] $NOEL_{mortality}$ and $NOEL_{any\ effects}$ were not reported or could not be ascertained from the given information.

4.2.2 Inhalation toxicity

A large amount of information is available for HCN inhalation acute toxicity in humans and experimental animals. Exposure to lethal or near lethal doses in humans results in respiratory, cardiovascular and neurological symptoms, followed by coma and death. Death is due to respiratory failure or cardiac arrest (Gezondheidsraad 2002, ATSDR 2006). Symptoms occurring from substantial HCN inhalation typically occur within seconds (HPA 2011). The central nervous system is the primary target for cyanide toxicity.

The acute toxicity of cyanide in humans following inhalation has a steep dose-response relationship. Exposure for several hours to 20-40 mg HCN/m^3 may only lead to slight effects indicative of hypoxia (e.g. nausea, dizziness, headache). Whereas exposure to 120 mg HCN/m^3 may be fatal after 30 minutes to an hour (Gezondheidsraad 2002, WHO 2004, ECETOC 2007). After a single, brief exposure to a low concentration of HCN from which an individual recovers quickly, no long term health effects have been observed (HPA 2011, NICNAS 2010, NPS 1997). However, serious acute

[16] Scopoletin is a potent hypotensive and spasmolytic agent which has been isolated from cassava roots and may contribute to the tropical ataxic neuropathy observed among cassava eaters.

cyanide poisoning, from inhaling a high concentration, that does not result in death may be associated with severe neurotoxicity (Parkinsonism[17] and morphological damage in the brain) (US EPA 2010, ECETOC 2007). Despite the high lethal potency of acute inhalation exposure to high HCN concentrations, repeated sublethal exposures seldom result in cumulative adverse effects (ECETOC 2007). In fact, it is reported substantial but sublethal intermittent concentrations (details for doses not provided) of HCN can be tolerated by many animals for long periods without adverse effects (NPS 1997).

Inhalation lethality and non-lethality data obtained from laboratory animals is summarised in Tables 3.5 and 3.6 (see Section 3.1.2). LC_{50} for HCN ranges from 133 (60 min, rat) to 3,800 mg HCN/m^3 (12 seconds, rat) depending on test species and exposure time.

Based on case report studies, ATSDR (2006) estimated the acute median lethal exposure level in humans to be 579 mg/m^3 for a 10-minute inhalation exposure to HCN. However details of how this was derived are not provided. .

Nonlethal acute exposures to HCN gas in workers is reported to cause upper respiratory irritation, cough, altered sense of smell, nasal congestion, epistaxis (nosebleeds), hemoptysis (expectoration of blood from lungs), and dyspnoea (ATSDR 2006). The levels of exposure in these cases were not provided.

4.2.3 Dermal toxicity

The dermal LD_{50} for HCN, NaCN or KCN in rabbits ranges from 2.3 to 22.3 mg CN/kg (see Table 3.7, Section 3.1.3), depending on the cyanide compound and whether it was applied to intact or abraded skin. Rabbits exhibited tremors and convulsions preceding death. Dry NaCN powder (200 mg CN/kg) on intact dry skin did not result in absorption of cyanide in amounts sufficient to produce signs of systemic toxicity. Rapid breathing and minor convulsions (only observed in 1 of 4 guinea pigs) also preceded coma and death in guinea pigs exposed dermally to unknown doses of HCN (Fairley et al 1934). Rieders (1971, as cited in ATSDR 2006) estimated an average dermal LD_{50} value of 100 mg CN/kg as HCN for humans. The original publication was not available to ToxConsult, and ATSDR (2006) did not provide the derivation for this value.

[17] The Parkinson-like symptoms may include generalised rigidity, bradykinesia, tremors of tongue and eyelids, slow-shuffling gait, and a weak dysphonic voice. Not all Parkinsonian symptoms are manifested.

Breathing irregularities including Cheyne-Stokes respiration developed in two people who fell into cisterns containing hot CuCN or KCN[18] (Dodds and McKnight 1985; Trapp 1970) and one person whose hands were exposed to liquid HCN[19] (Potter 1950). All three became comatose but eventually recovered after treatment. The person that fell into the CuCN cistern[20] also developed cardiovascular (peripheral vasoconstriction and gross plasma extravasation) and renal (scanty urination) effects (Dodds and McKnight 1985). The worker exposed to HCN complained of dizziness and difficulty breathing before falling into a coma a few minutes after exposure. There were no cuts or abrasions on his hand (Potter 1950).

Cardiovascular effects (palpitations) and neurological effects (dizziness, weakness, headaches) were also recorded in three men who wore respiratory masks while working in an atmosphere containing 22,100 mg/m^3 HCN for 8-10 minutes; the masks were reported to give excellent respiratory protection, therefore the effects are likely due to dermal exposure (Drinker 1932, as cited in ATSDR 2006).

Murray et al (1987, as cited in ECETOC 2007) reported 27 cases of cyanide poisoning registered in the UK from 1963 to 1984 upon skin contact (one case due to organic cyanide), eye contact or combined oral and skin exposure. No further details are available. Apparently there were no fatalities.

4.2.4 Acute exposure guidelines

Food Standard Australia New Zealand (FSANZ) and the Joint FAO/WHO Expert Committee on Food Additives (JECFA) have derived acute reference doses (ARfD) for linamarin (the predominant cyanogenic glycoside in cassava) of 0.7 mg/kg body weight (i.e. 80 µg HCN/kg bw) and 0.9 mg/kg bw (i.e. 90 µg HCN/kg bw), respectively. Their basis and derivation is described in Appendix A.

However, as the rate of release of CN^- from linamarin ingested in cassava is likely to be different from the rate of release of CN^- from metallo-complexed WAD cyanide, the applicability of the ARfD for linamarin to Dargues Mine is uncertain.

[18] Concentration of cyanide not reported. The vat was reported to contain AgCN, KCN – 12 ounces (i.e. 340 g) to each of the 150 gallons (i.e. 570 L) and NaOH (Trapp 1970).

[19] Concentration of HCN not reported (Potter 1950).

[20] Concentration not reported. The person remained in the cistern (containing approx. 3,800 L of hot CuCN) for 3 minutes before being rescued and rushed to hospital emergency care.

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4.3 Subchronic toxicity

4.3.1 Oral toxicity

In subchronic animal studies where NaCN or KCN were administered orally in the diet or water:

- reproductive toxicity in male rats (e.g. reduced absolute epididymal weight, testicular weight, sperm count) was observed when orally exposed to 12.5 mg CN^-/kg/d for 13 weeks (NTP 1993) (with no tissue effects at 0.5 or **4.5 mg/kg/d**)[21]. The examination of neurotoxicity in this study consisted of clinical observations and examination of brain (but not spinal cord) in autopsy[22].
- Hepatic toxicity[23] was observed in rabbits exposed to sodium cyanide at doses of 15 mg CN^-/kg/d for 4 weeks or 24 mg CN^-/kg/d for 40 weeks (Okolie and Iroanya 2003, Okolie and Osagie 1999),
- Potential neurotoxicity[24] in rats given 30 mg CN^-/kg/d for 11.5 months (Philbrick et al. 1979)[25].

[21] NTP (1993) administered NaCN in drinking water for 13 weeks to rats at concentrations of 0, 0.16, 0.48, 1.4, 4.5 and 12.5 mg CN^-/kg/day in male rats; and 0, 0.16, 0.53, 1.7, 4.9 and 12.5 mg/kg/d in female rats. A statistically significant decrease in cauda epididymis weight (7%) was seen at doses ≥1.4 mg/kg/day. A 7% decrease in whole epididymis weight (as compared to cauda epididymis) was seen at 12.5 mg/kg/d. At the highest dose tested (12.5 mg/kg/d), epididymis and cauda epididymis weights were decreased by 7 and 13%, respectively. Dose-related decreases in testis weight (8%), number of spermatid heads (14%), and spermatid concentration (14%) were also found to be significant at doses ≥12.5 mg/kg/d. A statistically significant decrease in epididymal sperm motility was observed at doses ≥1.4 mg/kg/d, although it did not appear to increase in severity with dose. US EPA (2010) considered 1.4 mg/kg/d a Low Observed Adverse Effect Level (LOAEL), in contrast to ATSDR (2006), who considered 4.5 mg/kg/d to be a NOAEL. ATSDR (2006) considered the reductions in cauda epididymis weights observed at 1.4 and 4.5 mg/kg/d were not biologically significant in the absence of any other significant effect. They also considered the small (<4%) statistically significant, but not dose-related, reductions in sperm motility in the 1.4, 4.5 and 12.5 mg/kg/d groups were within the range of normal values and not biologically significant (ATSDR 2006). DEFRA (2002) came to the same conclusions as ATSDR (2006).

[22] Parameters evaluated included body weight, clinical signs, water consumption, clinical chemistry, haematology, urinalysis, extensive histopathology, selected organ weights (heart, kidneys, liver, lungs, thymus gland, testes, epididymis, causa epididymis), testicular sperm measures (spermatid count and heads), epididymal sperm measures (spermatozoa count and motility) and vaginal cytology.

[23] Signs of hepatic toxicity consisted of significant decreases in activities of superoxide dismutase and catalase (Okolie and Iroanya 2003) or alkaline phosphatase, glutamate pyruvate transaminase and sorbitol dehydrogenase (Okolie and Osagie 1999) in the liver compared to controls. Also observed were a number of histopathological indicators for liver toxicity (necrosis, fatty degeneration and congestion).

[24] Signs of neurotoxicity were modest myelin degeneration of spinal cord tracts in treated rats. Due to tissue autolysis, it could not be determined whether these changes resulted from histotoxic anoxia or an alteration of oligodendroglial myelin metabolism.

[25] The dose in Philbrick et al. (1979) provided here is as cited by ATSDR (2006). Upon consultation of Philbrick et al. (1979), the paper does not provide a dose or consumption information, only an average weight for rats (43g) (this weight indicates they were juvenile animals) and the concentration of KCN in diet (1500 ppm).

4.3.2 Inhalation toxicity

No data are available for the subchronic inhalation toxicity of HCN in humans and only little data available in animals. One study reported 25% mortality, and serious neurological effects (tremors, ataxia), respiratory effects (dyspnoea), and gastrointestinal effects (vomiting, tenesmus[26], diarrhoea) in dogs exposed to 45 ppm (i.e. 50 mg/m^3) HCN for 30 minutes/day, every other day for 28 days (Valade 1952, in ATSDR 2006). A No Adverse Effect Level (NOAEL) could not be established.

4.3.3 Dermal toxicity

No data were found for the subchronic dermal toxicity of cyanide in humans or animals.

4.3.4 Subchronic exposure guidelines

ATSDR (2006) derived an intermediate-duration (15-364 days) minimal risk level (MRL) of **0.05 mg CN^-/kg/d** from a No Observed Adverse Effect Level (NOAEL) of 4.5 mg/kg/d in the NTP (1993) rat 13 week oral study with sodium cyanide.

The World Health Organisation (WHO 2009, 2011) have derived a 'short-term' (i.e. <5 day exposure) drinking water quality guideline for cyanide of 0.5 mg/L, applying to total cyanide concentration at the tap. The Australian National Health and Medical Research Council (NHMRC) also derived a drinking water guideline for cyanide (NHMRC 2013). The guideline is 0.08 mg/L. Since NHMRC have not defined an acute or intermediate exposure timeframe to which the guideline applies, it is assumed it applies to chronic exposure. The derivation of the various guidelines available for cyanide is provided in Appendix A.

4.4 Chronic toxicity and associated exposure guidelines

The chronic (repeat-dose) toxicity of cyanide in humans is mediated through the main metabolite and detoxification product, thiocyanate (WHO 2004, ECETOC 2007). Several occupational studies in workers in electroplating jobs describe serious neurological, respiratory, cardiovascular, and thyroid effects following inhalation exposure of 6.4-15 ppm (7-16.6 mg/m^3) for a long time (ATSDR 2006). These studies were limited due to lack of exposure information, the small size of cohorts, and additional dermal contact with cyanide in liquids. Neurological effects were also noted in workers receiving exposure from copper cyanide but they also had exposure to gasoline and hydrochloric acid). ATSDR (2006) considered the studies inadequate for deriving chronic inhalation MRLs for cyanide.

[26] A feeling of constantly needing to pass stools.

In a 2-year feeding study, rats were provided with food that had been fumigated with HCN. The food was provided in customised jars to limit loss by volatilisation (Howard and Hanzal 1955). HCN intakes for exposed animals[27] were 4.3 mg/kg/d and 10.8 mg/kg/d (in females). No treatment related effects were observed at either dose on survival, growth rate, clinical signs, haematological or histopathological changes in the organs examined[28]. A NOAEL of 10.8 mg/kg/d was established (Howard and Hanzal 1955, WHO 2004). However, ATSDR (2006) considered the study to be of low reliability because evaporation of cyanide from the feed resulted in unstable cyanide levels throughout the experiment and uncertainties as to the dose response for cyanide.

Long-term consumption of cassava containing high levels of cyanogenic glycosides, when constituting the principal food source, has been associated with tropical ataxic neuropathy[29], spastic paraparesis (collectively termed 'konzo'), and, in areas with low iodine intake, development of hypothyroidism, goitre, and cretinism (WHO 2004, ATSDR 2006, US EPA 2010, ECETOC 2007). In some cases endemic exposure to cyanide has been crudely estimated to be 15-50 mg/day. However, due to limitations of exposure data and potential impact of confounders (e.g. malnutrition, low protein content of diet, vitamin deficiency, iodine status), WHO (2004) and US EPA (2010) concluded the available data do not provide meaningful information for use in hazard assessment or the dose-response of cyanide in humans. ATSDR (2006) also considered studies of populations eating cassava inappropriate for MRL derivation as some of the neurological effects observed may be the result of another compound occasionally found in cassava (i.e. scopoletin) rather than released cyanide. The agency therefore did not derive a chronic oral MRL due to the lack of suitable data in both animals and humans (ATSDR 2006).

JECFA established a provisional maximum tolerable daily intake (PMTDI) of 20 µg CN/kg/d (JECFA 2011) based on a $BMDL_{10}$ of 1.9 mg/kg/d for reduced absolute cauda epididymis (in testes) weights from the 13-week NTP drinking water study in rats with sodium cyanide (NTP 1993). US EPA (2010) has also derived a chronic exposure guideline of 0.0006 mg/kg/d (i.e. 0.6 µg/kg/d) for cyanide using the data from the same study used by JECFA (i.e. NTP 1993) but a larger uncertainty factor.
The PMTDI from JECFA (2011) is based on the 13 week NTP (1993) study using NaCN. The study is therefore appropriate for the toxicological forms of cyanide that could be present in the Dargues Mine TSF. In addition, the effect on which the PMTDI is based is very sensitive (small decrease in cauda

[27] Intakes in mg/kg/day as reported by WHO (2004), calculated based on data for concentrations at the beginning and end of each food preparation and by assuming first-order rate of loss for the intervening period.

[28] Organs examined were heart, lung, liver, spleen, GI tract, kidneys, adrenals, thyroid, testes, uterus, ovaries, cerebrum, cerebellum, and brain.

[29] Tropical ataxic neuropathy is a disease characterised by irreversible paraparesis. Patients usually give a history of almost total dependence on a monotonous diet of cassava derivatives. However, the role of cyanide exposure as the only causative agent is questionable (WHO 2004).

epididymis weight) and a 2-year feeding study in rats (Howard and Hanzal 1995, described previously), albeit it had limitations, did not find adverse effects at treatments similar to those used in the NTP (1993) study. It is also understood that sustained, lower-level exposures to cyanide are better accommodated by detoxification mechanisms in animals than high exposures which may exhaust the detoxification capacity. By spreading the applied dose over a longer exposure period a higher total dose per day may be tolerated (ECETOC 2007). Hence the high uncertainty factor used by the US EPA (2010) may be excessively conservative and unwarranted.

The National Health and Medical Research Council (NHMRC 2013) used the results of a 6-month feeding study in juvenile pigs (Jackson 1988) to derive a drinking water quality guideline of 0.08 mg/L for cyanide (presumably to be measured as total, although this is not explicitly stated). The study that the NHMRC (2013) guideline was based on employed bolus dosing, a small number of animals, and limited statistical analysis which according to the US EPA (2010) and WHO (2004) limits its usefulness for guideline development. In addition, the biological significance of the behavioural changes observed in the study is unclear (WHO 2004, US EPA 2010).

The derivation of the various exposure guidelines for cyanide has been described in Appendix A. There is no evidence that cyanide is carcinogenic (although specific carcinogenicity studies are lacking) and studies assessing the genotoxicity of cyanide salts *in vitro* or *in vivo* have been negative (ATSDR 2006, Gezondheidsraad 2002, HPA 2010a, HPA 2011, JECFA 1992, US EPA 2010, ECETOC 2007, NPS 1997, WHO 1997). Similarly, cyanide has no structural alerts for DNA reactivity (HPA 2011). Cyanides have been embryotoxic and teratogenic only at maternally toxic doses, however Genzondheidsraad (2002) noted adequate reproduction toxicity studies are lacking.

4.5 Summary of existing guidelines/standards for cyanide

The following table is a list of existing health guidelines from various national and international authorities for cyanide. Their derivation has been briefly summarised in Appendix A.

Table 4.2: Existing (human) health guidelines for cyanide [a]

Guideline	Value (µg/kg/d)	Principal study	POD (mg/kg/d)	UF/CF	Source
Acute RfD	80 (diet)	Frakes et al. 1985	70 (NOAEL dams linamarin)	100/9.1	FSANZ 2008b, 2014
Acute RfD	90 (diet)	Frakes et al. 1985	85 ($BMDL_{10}$ foetuses linamarin)	100/9.1	JECFA 2011
Oral intermediate MRL (15-364 days)	50 (NaCN in drinking water)	NTP 1993	4.5 (NOAEL)	100	ATSDR 2006
PMTDI	20	NTP 1993	1.9 ($BMDL_{10}$)	100	JECFA 2011
Chronic RfD	0.6	NTP 1993	1.9 ($BMDL_{1SD}$)	3,000	US EPA 2010
Drinking water guideline, Australia	80 µg/L	Jackson 1988	1.2 (NOEL)	100 (plus other assumptions: 70 kg bw, 2L/d intake, 20% from DW)	NHMRC 2013
Drinking water guideline, WHO (short-term exposure, <5d)	500 µg/L	NTP 1993	4.5 (NOAEL)	100 (plus other assumptions: 60 kg bw, 2L/d intake, 40% from DW)	WHO 2009, 2011

POD = point of departure, UF = uncertainty factor, CF = conversion factor (e.g. from mass of linamarin to mass of cyanide), RfD = reference dose, NOEL = No Observed Effect Level, NOAEL = No Observed Adverse Effect Level, MRL = minimal risk level, PMTDI = provisional maximum tolerable daily intake.

[a] The derivation of these guidelines has been briefly summarised in previous sections of the text (see Sections 4.2.4, 4.3.4 and 4.4).

4.6 Key Points from Section 4

- *Cyanide is a potent and rapid-acting chemical asphyxiant by inhibiting cytochrome C oxidase.*
- *The toxicity of individual cyanide compounds is dependent on the ease with which they release free CN^-. For example, stable Fe cyanide complexes are nearly non-toxic.*
- *After ingestion of cyanide salts or metal complexes cyanide is absorbed as HCN. Different amounts of HCN are formed in the gastrointestinal tract depending on the form of cyanide.*
- *CN^- is readily and largely completely absorbed by humans after inhalation, dermal and oral exposure.*
- *HCN does not accumulate in the blood or tissues following chronic or repeat exposure. HCN is metabolised by the enzyme rhodanase to thiocyanates, which is readily excreted in urine.*
- *In humans, the plasma half-life for cyanide to be metabolised to thiocyanate is 20-60 minutes. The elimination half-life of orally administered thiocyanate is about 3 days in healthy human volunteers or 7-9 days in subjects with impaired renal function.*

Acute toxicity

- *Acute toxicity of cyanide in humans has a steep dose-response relationship. Exposure to lethal or nearly lethal doses rapidly (within seconds to minutes) leads to a series of respiratory, cardiovascular and neurological symptoms, followed by coma and death. Death is due to respiratory failure or cardiac arrest.*
- *After a single, brief exposure to a low concentration of HCN from which an individual recovers quickly, no long term health effects have been observed.*
- *However, serious acute cyanide poisoning that does not result in death may lead to severe and potentially irreversible neurotoxicity. There is no indication from the available data that repeated low dose exposure to cyanide could have similar effects. Substantial but sublethal intermittent doses of cyanide can be tolerated by many animals for long periods of time without adverse effects.*
  FSANZ (2014) and JECFA (2011) have set acute reference doses for cyanide (80 and 90 µg HCN/kg, respectively) using the same experimental study where pigs were fed the cyanogenic glycoside linamarin, but used different endpoints.

Subchronic toxicity

- *ATSDR (2006) derived an intermediate-duration (15-364 days) minimal risk level (MRL) of 0.05 mg CN^-/kg/d from the NOAEL of 4.5 mg/kg/d for reduced epididymal weight in male rats in a 90-day oral study from the NTP (1993) with sodium cyanide.*

- *The same point of departure was used by the World Health Organisation (WHO 2009, 2011) to derive a drinking water quality guideline of 0.5 mg/L for total cyanide (for short term exposure, i.e. <5 days).*

Chronic toxicity

- *JECFA (2011) and US EPA (2010) have both established chronic guideline values for cyanide (20 and 0.6 µg CN/kg/d, respectively). Both values used the same point of departure ($BMDL_{10}$ or $BMDL_{1SD}$ of 1.9 mg/kg/d for decreased cauda epididymis weight in rats from the NTP study with sodium cyanide) but applied different uncertainty factors resulting in a 33-fold difference in the derived guideline values. Since the effect on which the guidelines are based are very sensitive (small decrease in cauda epididymis weight) and a 2-year feeding study in rats did not find adverse effects at treatments similar to those used in the NTP (1993) study, the high uncertainty factor used by the US EPA (2010) is not justified and too conservative. Thus the JECFA (2011) guideline is considered more appropriate.*

- *There is no evidence that cyanide is carcinogenic (although specific carcinogenicity studies are lacking). Studies assessing the genotoxicity of cyanide salts in vitro or in vivo have been negative.*
- *Cyanides are embryotoxic and teratogenic at maternally toxic doses.*

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