	dysfunction, etc. **(6)**; Schultz, 1984 **(70)**; US EPA, 1990 **(71)**; ATSDR, 1993 **(7)**. Reference (**2**) reported a study of 35 male cyanide workers (of 201 male workers) who had worked in an Indian electroplating process of a cable industry for more than 5 consecutive years. Thirty-five non-exposed workers who had worked outside the manufacturing building were matched with the exposed workers for age and dietary habits. The mean serum thiocyanate concentration of the 35 non-smoking exposed employees was 316 ± 15 µmol/litre, which was significantly higher ($P < 0.01$) than that of the control subjects (90 ± 9.02 µmol/litre). Cyanide exposure resulted in a decrease of serum T4 and T3 concentrations ($P < 0.05$) and an increase in TSH concentration ($P < 0.05$) compared with the control subjects. A case of cerebrovascular accident and hyperthyroidism with struma and another with struma and hypothyroidism were reported among metal case- 1 Apparently as a typographical error, all referents were also listed as "diseased" hardeners. No information on the level of exposure to cyanide was given **(9)**. Reference **(10)** reported a cross-sectional study, carried out between April and September 1986, of the health of sodium, copper, and potassium cyanide salt production workers from plants in a facility in the United Kingdom. Sixty-three employees from these cyanide salt plants were compared in a controlled study with 100 employees from a diphenyl oxide plant in the same facility. The breathing-zone cyanide concentrations ranged between 0.01 and 3.6 mg/m^3. Cyanide workers were examined before and after a block of six shifts in the spring and autumn, while diphenyl oxide workers were seen during their shifts. Haemoglobin and lymphocyte levels tended to be higher in the cyanide workers, although neither was pathologically raised, and no relationship between exposure and haematological findings was found. The absence of a dose response relationship would suggest that cyanide work was not causal. Thyroid function was normal in both groups, and no goitres were found. Vitamin B12 and T4 levels revealed no differences between cyanide and diphenyl oxide exposure groups. Biochemical effects of occupational and dietary exposure to cyanide were investigated in a preliminary study of cyanide poisoning from large-scale cassava processing and ingestion of cassava foods in Nigeria **(11)**. The study population included 20 volunteers (female non-smokers, 24–50 years old and without overt signs of sickness or disease; 10 were cassava processors, 5 were "frequent" consumers of cassava, and 5 were "infrequent" consumers of cassava). The mean urinary thiocyanate level of the cassava processors (mean ± SD: 153.50 ± 25.2 µmol/litre) was 2.2 and 2.6 times higher than that of frequent (mean ± SD: 70.1 ± 21.8 µmol/litre) and infrequent (mean ± SD: 59.3 ± 17.0 µmol/litre) cassava consumers, respectively. Any increase in plasma activity by 10% above normal ASAT (not statistically significant) was observed in 40% of the cassava processors, whereas it was within normal range in all consumers. No change was observed in the ALAT, alkaline phosphatase, or serum creatinine values. There are no reported data on the carcinogenicity of cyanides in exposed human populations: **ATSDR** (1997, Toxicological profile of cyanide) **(DOC IV_1)** and **IPCS** (2004, WHO, CICAD 61: Hydrogen cyanide and cyanides: human health aspects). **(DOC IV_5)** and Hazardous Substance Data Bank (**HSDB**), National Library of Medicine´s TOXNET system (state in February 2006): Hydrogen cyanide *Peer reviewed* **(DOC IV_2)**
Partial conclusions	1. Hydrogen cyanide vapours are absorbed through skin and mucous membranes surface. They are hazardous and toxic when inhaled but also when the skin is exposed. 2. Chronic occupational exposure to hydrogen cyanide *per se* resulting in serious injury is rather rare. Symptoms of such poisonings include headache, dizziness, confusion, muscular weakness, poor vision, slurred speech, gastrointestinal tract disturbances, trauma, and enlarged thyroid. 3. Workers exposed to HCN concentrations 5 – 13mg/m^3 for seven years

	showed in a large extent subjective symptoms (headache, weakness, ao). 4. A study in workers exposed to HCN concentrations approximately 17 mg/m^3 revealed a high prevalence of neurological, cardiovascular and gastrointestinal symptoms. 5. Thyroid enlargement is probably caused by thiocyanate, the main metabolite of cyanide. This has been observed in workers exposed to low concentrations in air for two years. No changes in thyroid functions (and no other biochemical or haematological deviations) were found if breathing-zone cyanide concentrations ranged between 0.01 and 3.6 mg/m^3.

Clinical observations, General population exposures **Toxicokinetic data**	**CLINICALLY RELEVANT TOXICOKINETIC DATA:** ***Levels in blood:*** Non-smokers < 0.02µg/ml Smokers – average – 0.041µg/ml (**12**) Exposure level < 0.2µg/ml is not toxic. Any level between 0.5 and 1.0µg/ml may cause tachycardia and nervousness. Toxic level between 1.0 and 2.5µg/ml may cause desensitisation. Levels above 2.5µg/ml cause coma, respiratory depression. Levels above 3µg/ml cause death. (**13**) ***Levels in serum or plasma:*** Normal non-smokers 0.004µg/ml (exposure level not determined) smokers 0.006µg/ml (exposure level not determined) Toxic higher than 0.1µg/ml ***Distribution – inhalatory exposure*** Absorbed hydrogen cyanide is quickly distributed by blood into the whole body. Levels of hydrogen cyanide measured were 0.75, 0.42, 0.41, 0.33 and 0.32mg/100g tissue in lungs, heart, blood, kidneys and brain; the values come from a male who had died after inhalatory exposure to hydrogen cyanide. In one case of death caused by oral exposure to hydrogen cyanide, oral exposure was estimated at 30mg HCN in food approx. 3 hours before the death. **(72)** ***Distribution – oral exposure*** No data for hydrogen cyanide are available. ***Distribution - dermal exposure*** No study on HCN distribution in a human body after dermal exposure has been found. ***Metabolism*** Approximately 80% of absorbed cyanides are metabolised due to the action of mitochondrial enzyme rhodanese which catalyses the transfer of thiosulphate sulphur to cyanide with the formation of thiocyanate. **(14,73)**
Acute toxic doses and levels	**ACUTE TOXIC DOSES AND LEVELS:** The dose–effect curve of the acute effects in humans is steep. Whereas slight effects occur at exposure to hydrogen cyanide levels of 20–40 mg/m^{3}3, 50–60 mg/m^{3}3 can be tolerated without immediate or late effects for 20 min to 1 h, 120–150 mg/m^{3}3 is dangerous to life and may lead to death after 0.5–1 h, 150 m^{3}g/m3 is likely to be fatal within 30 min, 200 mg/m^{3}3 is likely to be fatal after 10 min, and 300 mg/m^{3}3 is immediately fatal **(69)**.

Clinical observations	**Acute inhalatory exposure** Average fatal concentration for human organism has been estimated at 564ppm HCN at 10min exposure. **(15)** In other cases, exposure to 270ppm HCN caused immediate death.(**4**) Exposure to 181ppm was fatal after 10 minutes, and exposure to 135ppm was fatal after 30 minutes. **(4)** *Effect* — *Concentration* Immediate death — 300mg/m^3 Death in 10 minutes — 200mg/m^3 Death in 30 minutes — 150mg/m^3 Highly dangerous in 30-60 minutes — 120-150mg/m^3 Tolerable for 20-60 minutes — 50-60mg/m^3 Slight symptoms of poisoning in several hours — 20-40mg/m^3 **(69)** **Acute dermal exposure** Estimated *lethal* value LD_{50} for humans is 100mg CN^-/kg, calculated as HCN.(**16**) **DIRECT OBSERVATIONS, CLINICAL CASES AND POISONING INCIDENTS:** Superacute (swift) poisoning is the result of an unexpected high concentration of HCN, with unconsciousness occurring within only 10-20 seconds, followed by death in convulsions within 2-3 minutes. Visible pink colouring of skin and mucous membranes. Acute poisoning symptoms include headache, dizziness, vision disorders, pressure in chest, rapid breathing and pulse, followed by asphyxiation and unconsciousness, and clonic and tonic convulsions. Pupils are dilated and skin covered with cold sweat, and finally respiratory and cardiac arrest. Mild poisoning symptoms include headache, dizziness, hearing problems, sore throat, and vision impairment and breathing problems. The patient is fully conscious and complete recovery is possible. Irritating properties of vapours (gas): HCN vapours are not very irritating. Irritating properties of liquid: the liquid is not too irritating; however it is extremely toxic if absorbed through lungs, skin or eyes. No data on eye irritation are available. Long-term (chronic) exposure to HCN may cause conjunctivis or surface keratitis. Poisoning symptoms appear within several seconds to minutes after inhalation or ingestion of vapours. They include: dizziness, deep breathing, headache, palpitation, cyanosis, asphyxia, unconsciousness, and convulsions followed by death.
Acute poisoning symptoms	**Symptoms of poisoning:** 1. High exposure (high dose) may lead without any warning to sudden unconsciousness and respiratory arrest resulting in immediate death. 2. With lower, but still lethal exposure (dose), the poisoning symptoms may be delayed for one to several hours. Ingestion is followed by bitter, pungent, burning taste quickly getting stronger, and by contraction and desensitising of oesophagus. Salivation, nausea and vomiting may also occur. 3. Anxiety, confusion, dizziness and often feeling of stiffness of lower jaw. 4. Deep breathing and breathlessness. Breathing is very fast and then slow and irregular. Typically, breathe in is short, while breathe out very long. 5. Bitter almonds odour in breath or vomitus. 6. Early phase of poisoning includes an increasing vasoconstrictor tonus (narrowing of blood vessels), which is a cause of increased blood pressure

Lethal effects	and slowed heart pulse. Pulse gets faster, weaker and irregular. Accumulation of oxyhaemoglobin in venous blood causes bright pink colouration of skin and may be confused with carbon monoxide poisoning. (**17**) 7. Strong convulsions are quickly followed by unconsciousness, sometimes accompanied by involuntary emptying. 8. Convulsions lead to paralysis. Skin is covered with sweat, eyes are bulging, and pupils are dilated and unresponsive. Froth appears at the mouth, sometimes mixed with blood. Skin may have brick-red colour. Cyanosis may not be apparent despite weak, irregular breathing. Unconsciousness may be accompanied by bradycardia, and cyanosis absence may be crucial for determining diagnosis. 9. Death caused by respiratory failure – if heart is still beating – may be reversed if immediate resuscitation and medical help are applied. (**18**) Serious HCN poisoning begins with quick onset of toxic effects including fainting, seizure, respiratory coma and cardiovascular failure, which may cause death within several minutes. Cyanide poisoning in humans has two signs. Insufficient consumption of molecular oxygen in peripheral tissues is the result of a high concentration of oxyhaemoglobin in venous blood and causes brick-red or pink colouring of the skin. The organism is trying to even the oxygen exchange inhibition which leads to increased requirements of glycolysis which is responsible for metabolic acidosis. (**19**) The most specific aspect of acute poisoning by hydrogen cyanide is bright red colour of venous blood (pathological examination), clear evidence of the tissue cells inability to utilise oxygen. After recovery from hydrogen cyanide poisoning so called after effects may occur for long time: physical and mental tiredness, muscular hypotonia, ataxia and a number of nervous and mental disorders. **(74)** **Oral exposure** Oral exposure by gaseous hydrogen cyanide is beyond consideration. No studies of oral toxicity have been published. Minimal oral fatal dose of HCN for humans is estimated at 50mg. (**20**) **Inhalatory exposure** Based upon U.S. military data, HCN concentration 613mg/m^3 is an average concentration which kills humans within 10-minute inhalatory exposure. Concentration 303mg/m^3, documented in industrial accidents, proved to kill humans immediately. Concentration 203mg HCN/m^3 caused death within 10 minutes, concentration 152mg/m^3 caused death within 30 minutes. Inhalation of an adequate quantity of gaseous hydrogen cyanide causes quick death; HCN was used in this way for execution in gas chambers. **(21)** Average fatal concentration for human organism has been estimated at 564ppm HCN at 10min exposure (**15**). In one case a worker was exposed to 200ppm in an electrolytic tank, fell unconscious and despite having been administered antidotes eventually died in hospital. **(22)**. In other cases, exposure to 270ppm HCN caused immediate death, exposure to 181ppm was fatal after 10 minutes, and exposure to 135ppm was fatal after 30 minutes. **(4)** **Dermal exposure** Estimated LD_{50} value for humans is 100mg CN^-/kg, calculated as HCN (**16**). **First aid and and treatment of acute poisoning** See section 8.5.2.

Cases of lethal effects	**CASE STUDIES** A fire fatalities study in Maryland, USA, covering mostly residential fires over a 6-year- period during which 523 fire fatalities occurred as a result of 392 fires, was reported **(23)**. Although the predominant cause of death was attributed to carbon monoxide, toxic levels of hydrogen cyanide were found in the blood of a substantial percentage of the victims. A study of blood cyanide and carboxyhaemoglobin concentrations in 18 victims found dead in buildings after fires indicated that 50% of the victims had been exposed to toxic levels of hydrogen cyanide and 90% to toxic levels of carbon monoxide **(24)**. Eighty-eight per cent of the fatalities in fire deaths in Glasgow, Scotland, during the period 1976–1979 had elevated blood cyanide levels; 31% had toxic levels of cyanide, and 12% would have shown severe cyanide **(25)**. Ref. **(26)** reviewed the carboxyhaemoglobin and cyanide in blood of fire and non-fire victims resulting from 15 major episodes during the years 1971–1990 in France, the USA, and the United Kingdom. Analysis revealed that hydrogen cyanide is likely to be present in appreciable amounts in the blood of fire victims in modern fires. A review of the resultant mechanism of action of acute carbon monoxide and cyanide exposure and how they may interact concluded that it remains difficult to attribute death in fires to inhalation of hydrogen cyanide per se, given the complexity of interactions of smoke components (principally carbon monoxide). A man died on a fishing vessel after being exposed to toxic vapours from rotten fish which contained lethal concentrations of hydrogen cyanide, carbon monoxide and hydrogen sulphide. All collapsed after 1 minute of exposure. Exposure to cyanides was confirmed by biopsies, with concentration 0.05mg/l cyanides found in their blood. **(64)**. Acute exposure to cyanide has occurred most frequently by the oral route from attempted suicides and homicides by ingestion of sodium or potassium cyanide or by accidental poisonings due to ingestion of apricot kernels or almond seeds (Rieders, 1971 **(16)**; NIOSH, 1976 **(27)**; US EPA, 1990 **(71)**; **(8)**; Alarie, 2002 (**26**). Based on analyses of cyanide contents in tissues and in gastrointestinal tract contents among fatal (oral) poisoning cases (and comparative kinetics with dogs) **(75)** estimated that death occurred after absorption of an average of 1.4 mg hydrogen cyanide/kg body weight; the lowest fatal absorbed dose was 0.54 mg hydrogen cyanide/kg body weight. In most poisonong cases, a large part of the ingested cyanide remained in the gastrointestinal tract (thus, using the dose ingested as an indicator of the lethality of cyanide is misleading). Some individuals ingesting 1–3 g of cyanide salts have survived **(8)**.
Cases of non-lethal effects **Inhalation**	**EFFECTS OF INHALATORY EXPOSURE ON INDIVIDUAL SYSTEMS** ***Respiratory tract effects*** Symptoms of poisoning appears within several seconds to several minutes after ingestion or inhalation of vapours. These include: dizziness, deep breathing, headache, palpitation, cyanosis, unconsciousness, asphyxiation, and convulsions which may be followed by death (**28**). According to patients acutely exposed to hydrogen cyanide and treated in hospital, stimulation of breathing appears first followed by asphyxiation. **(29)**; **(28)**. Exposure levels at the accidental intoxication were not available. Nasal mucous membrane irritation was observed in volunteers exposed to 16ppm HCN (8ppm cyanide) for 6-8 minutes. No effects were observed with concentration of 8ppm HCN (4ppm cyanides) **(76)**. Dyspnea was observed in workers chronically exposed to 6.4-10ppm of unspecified cyanide for 5-15 years. The exposure occurred during electrolytic galvanising, the process may have liberated sodium cyanide and copper cyanide **(67)**, and in workers exposed to 15ppm hydrogen cyanide in silver regeneration plants. **(68)** Other problems include coughing, sore throat, changes in smell perception, blocked

	nose, nose bleeding and haemoptysis. However, these cases included also exposure to other chemicals used in electrolytic galvanising, as cleaning agents and cutting oils. ***Cardiovascular effects*** **Ref. 21** published a report about four persons executed by hydrogen cyanide (without stating its concentration). The author described distinct slowing of heartbeat within 1-3 minutes after exposure; further changes of the heart rate were connected to irregular sinus. The most common cardiovascular effects in patients after accidental exposure to HCN included palpitation and hypotension, but the exact exposure level was not known. **(28)** Workers exposed to cyanide concentrations 6.4-10.4ppm for 5-15 years (sodium cyanide and copper cyanide formed in electrolytic galvanising) complained about precordial pain. However, the process of electrolytic galvanising includes also exposure to other chemicals, as cleaning agents and cutting oils **(67).** Approximately 14% of workers exposed to 15ppm HCN in silver regeneration plants reported palpitation, and 31% of workers reported chest pains **(68).** ***Gastrointestinal tract effects*** Stomach rising or vomiting was observed in 69% of workers exposed to 15ppm HCN in silver regeneration plants **(68).** Vomiting was observed also in workers exposed to cyanide concentrations 6.4-10.4ppm for 5-15 years (occupational exposure to sodium cyanide and copper cyanide formed in electrolytic galvanising. However, the process of electrolytic galvanising includes also exposure to other chemicals, as cleaning agents and cutting oils **(67).** Effects of cyanides on gastrointestinal tract are probably caused by effects on the central nervous system and/or by irritation of gastric mucosa, which is also the case of ingesting the gas during breathing. **Haematological effects** Increase in haemoglobin and an increased number of lymphocytes were observed in workers exposed to unspecified cyanide concentrations 6.4-10.4ppm during electrolytic galvanising. These results significantly varied from those obtained from controls. In addition, *punctate basophilia* of erythrocytes indicating intoxication was present in 28 out of 36 persons. However, copper is known for its effects on blood in exposure and is also present in electrolytic galvanising. **(67)** Another study **(30)** reports an increased level of neutrophils; an increased rate of erythrocyte sedimentation and decreased level of haemoglobin were observed in male workers exposed to unspecified cyanide concentrations for an unspecified time during the hardening process in electrolytic galvanising. ***Effects on kidneys*** One study carried out with respect to effects on kidneys in humans at inhalatory exposure to cyanides describes anuria and polyuria in humans exposed to 200ppm HCN for unspecified time **(22).** ***Musculoskeletal effects*** After inhalation of HCN have not been described in literature. ***Hepatic effects*** After inhalation of cyanides included an increased level of serum alkaline phosphatase, but not an increased level of bilirubin (**30**). Inhalation of 200ppm HCN for an unspecified time caused anuria followed by polyuria **(22).** ***Endocrine system effects*** A group of persons exposed to 15ppm HCN showed increase of mean levels of TSH (thyroid stimulating hormone) **(68).**

	Persons long-term exposed to 6.4–10.5ppm HCN showed increase of thyroid gland. Endocrine effects were ascribed to the effects of thiocyanates formed by cyanide metabolising **(67).** ***Effects on skin*** Skin rash was observed in 42% persons exposed to 15ppm HCN **(68).** No skin effects were observed in persons exposed to long-term effects of 6.4–10.4ppm HCN. **(67)**. ***Effects on eyes*** A partial loss of peripheral vision was observed as a permanent effect of 13-minute exposure to 452ppm HCN. **(69)**. In other studies, eye irritation was observed at 15ppm HCN **(68)** and lacrimation at 6.4ppm HCN. **(67)** ***Effects on body weight*** Decreased appetite was observed in 58% persons exposed to 15ppm HCN, and body weight decrease in 50%. **(68)** ***Immune and lymphoreticular effects of*** HCN inhalation have not been described in literature. ***Neurological effects*** The primary target of HCN toxicity is the central nervous system. Inhalation of hydrogen cyanide causes first short-time stimulation followed by depression, convulsions, unconsciousness with elimination of basic reflexes and pupil dilatation, paralysis and death. Lower concentrations of HCN may cause dizziness, breathlessness, giddiness, languor and headache. As a distant effect, recent memory deterioration accompanied by convulsions was observed after a year from acute poisoning by hydrogen cyanide. **(68)**; **(28)**; **(22)**. After chronic exposure to 15ppm of HCN, increased tiredness, dizziness, headache, ear ringing, sleep disorders, limb cramps, and faintness were observed after unspecified time. Some neurological disorders continued even after ten months from exposure **(68)**. Other studies proved disorders including headache, weakness, changes in flavour and smell perception, nausea, concentration disorders and psychoses, loss of momentary as well as remote memory, worsening of visual abilities, of psychomotoric abilities and visual recognition Cyanides may cause blindness and damage optic nerves.
Dermal exposure	**EFFECTS OF DERMAL EXPOSURE ON INDIVIDUAL SYSTEMS** Dermal exposure is the second most severe type of exposure to hydrogen cyanide by which HCN may effect humans. No data concerning haematological, musculoskeletal, hepatic and endocrine effects, and effects on body weight, gastrointestinal system, skin, eyes, immune and lymphoreticular systems caused by dermal exposure to cyanides are available. ***Respiratory system effects*** A worker whose hands were exposed to HCN had subsequently problems with breathing. ***Cardiovascular system effects*** Palpitation was observed in three persons who had been working in 20,000ppm of HCN for 8–10 minutes only with protective masks (**3**). ***Renal system effects*** Occasional oliguria was observed in one person exposed (whole body) to a solution of copper cyanide for 3 minutes (**31**). ***Neurological effects*** Persons working in 20,000ppm HCN for 8–10 minutes with protective masks

All routes	experienced nausea, weakness and headache (**3**). ***Mutagenic effects*** No data on mutagenic effects of hydrogen cyanide on humans after oral, dermal or inhalatory exposure have been published. ***Carcinogenic effects*** No data on carcinogenic effects of hydrogen cyanide on humans after oral, dermal or inhalatory exposure have been published. ***Toxic effects on reproduction*** No data on toxic effects of hydrogen cyanide on human reproduction after oral, dermal or inhalatory exposure have been published. ***Sensitization*** No report of sensibilization or alergic reactions related to exposure to HCN was found.
Chronic toxicity General population epidemiological data	Data on chronic toxicity are mostly derived from occupational studies (as summarised above) or from general population studies on health effects of longterm consumption of food containing cyanogenic glycosides.
Food containing cyanogenic glycosides	Although acute cassava poisoning – sometimes leading to the death of whole families — has been occasionally reported after the consumption of inadequately processed cassava **(32), (33)** a much larger literature is available on the effects of long-term exposure to food containing cyanogenic glycosides. Clinical signs are often confounded by dietary deficiencies, including lack of protein, iodine, and vitamin B12. Accidental poisonings have been reported in children (and, exceptionally, in adults) who had ingested apricot kernels or seeds or candy made from apricot kernels containing D, L-amygdalin, which, after hydrolysis, yields cyanide **(34) (35) (36)**. Presumably because of lower body weight, children are especially vulnerable, with several fatal poisonings occurring after they had consumed apricot seeds. It has been estimated that, depending on the total cyanogenic potential of apricot seeds, 10 or more seeds could be fatal to a child **(37)**. Accidental choke cherry poisonings (attributed to D, L-amygdalin) have also been reported **(38), (39)**. Reference **(38)** described a case of a 56-year-old woman in Italy who was accidentally poisoned when she ingested choke cherries whose pulp contained cyanide (amygdalin). After recovery from coma, the patient showed signs resembling Parkinson disease, retrobulbar neuritis, and sensorimotor neuropathy. The choke cherries showed cyanide levels ranging from 4.7 to 15 mg/kg in the cherries and from 43 to 45 mg/kg in the spirit. The quantity of cyanide was reported to depend on the ripeness of the cherries and the year in which they were harvested. Consumption of food containing cyanogenic glycosides has been linked to several different diseases affecting mainly the nervous system, such as tropical ataxic neuropathy in Nigeria, spastic paraparesis (called mantakassa in Mozambique and konzo in the Democratic Republic of the Congo) in Cameroon, Central African Republic, Mozambique, Tanzania, and the Democratic Republic of the Congo (formerly Zaire), as well as retrobulbar neuritis and optic atrophy associated with pernicious anaemia. Cyanides have also been implicated in tobacco–alcohol amblyopia and thyroid effects such as goitre and even cretinism **(32)**; **(40)**; **(41)**; **(42)**; **(71)**; **(8)**; **(43)**; **(44)**; **(45)**; **(46)**. Tropical ataxic neuropathy, an upper motor neuron disease characterized by irreversible paraparesis **(46)**, was described in Nigeria in the 1930s, and dietary cassava was proposed to be the causative factor in 1934. The essential neurological components of the disease are myelopathy, bilateral optic atrophy, bilateral perceptive deafness, and polyneuropathy. The peak incidence is in the 5th and 6th decades of life, and the disease occurs rarely in children under 10 years of age. Patients usually give a history of almost total dependence on a monotonous diet

	of cassava derivatives. The plasma thiocyanate level in patients within 48 h of admission to hospital was 113 ± 0.2 µmol/litre, while in the referents it was 2.4 ± 0.15 µmol/litre **(32)**. However, the role of cyanide exposure as the only causative agent in tropical neuropathy is made questionable by the finding that when comparing two villages in Nigeria, one with a high prevalence (490/10 000) of tropical ataxic neuropathy and another with a low prevalence (17/10 000) (giving an age-adjusted prevalence ratio of 4), the estimated intake of cassava foods was higher in the latter, and no difference was observed in the urinary thiocyanate excretion between the two villages **(47)**. An epidemic of spastic paraparesis occurred in a drought-stricken cassava staple area of Mozambique in 1981–1982. Altogether, 1102 cases were identified. The highest recorded village prevalence rate found by active case detection was 29 per 1000 inhabitants; 65% of the cases were under 15 years of age. In contrast to tropical neuropathy, the onset of mantakassa was acute. General symptoms around the time of onset included fever, pain (especially in the legs), paraesthesiae, headache, dizziness, and vomiting; many patients also complained of weakness in the arms and difficulty in speaking and in seeing. Some mothers said that their children had difficulty in hearing. Neurological investigation revealed symmetrical spastic paraparesis of the lower extremities, symmetrically increased upper limb reflexes, diminished visual acuity, and dysarthria. Some of the patients had sensory changes as well. The mean hydrogen cyanide contents (mg/kg) of cassava from the affected area were as follows: fresh bitter cassava leaves, 377; fresh sweet cassava leaves, 347; fresh bitter cassava roots, 327; fresh sweet cassava roots, 138; dried bitter cassava roots, 95; dried sweet cassava roots, 46; cassava flour, 40; and cooked cassava, 10. The estimated intake of cyanide was 14–30 mg/day. The mean thiocyanate level in 246 specimens of blood and serum from patients from the whole area was 330 µmol/litre. In the village with the most patients, the mean thiocyanate level among the patients was 324 ± 18 µmol/litre, while 22 controls from this village showed serum thiocyanate levels of 288 ± 23 µmol/litre. There was no correlation between the disease severity and serum thiocyanate level. Also, because of the drought, there was a general lack of food, specifically of protein-rich food, with many cases of kwashiorkor1 appearing in February 1982 **(48)**. Outbreaks of konzo have been reported in the Democratic Republic of the Congo (formerly Zaire) since 1938. The outbreaks have occurred during droughts and dry seasons. Again, the affected populations have relied almost exclusively on bitter cassava roots as the staple food) **(49)**. In konzo-affected villages, the urinary thiocyanate levels were 563–629 µmol/litre during the dry season and 344–381 µmol/litre during the wet season; in reference villages without konzo, the levels were on average 241 µmol/litre. However, the urinary concentrations of linamarin showed a closer association with the disease than those of thiocyanate, and the authors interpreted it to indicate that more important than cyanide in the causation of konzo might be the neurotoxic action of linamarin itself **(50)**. Iodine deficiency and goitre, hypothyroidism, and cretinism are endemic in many areas of Africa. Several surveys in the endemic areas have demonstrated that there is also a strong correlation between cassava consumption and the thyroid effects **(51)**; **(52)**; **(53)**; **(54)**; **(55)**. A cassava meal also diminished the uptake of 131I in the thyroid **(52)**. A study in rural Mozambique found that in a population suffering from endemic spastic paraparesis, adequate iodine intake mitigated against the development of hypothyroidism or goitre, and high levels of dietary cyanogenic glycosides fom cassava could be tolerated **(56)**. Originally based on a geographical link between the prevalence of diabetes and cassava consumption **(57)**, dietary exposure to cyanides has been linked to the malnutrition-related diabetes mellitus **(58)**, also known as the "type-J" or "type-Z" diabetes **(59)**; **(60)**. The very existence of this third type of diabetes (in addition to the juvenile-onset and maturity-onset types) has been controversial **(61)**, and not all studies have detected a relationship between cassava consumption and diabetes prevalence **(62)**; **(19)**. The results of the standard glucose tolerance test were no more often abnormal among 88 Nigerian patients with tropical neuropathy than

	among 88 referents (**63**).
Conclusions	1) Hydrogen cyanide vapours are absorbed through skin and mucous membranes surface. They are hazardous and toxic when inhaled but also when the skin is exposed. 2) Clinical picture of acute hydrogen cyanide poisoning: Superacute poisoning is the result of an unexpected high concentration of HCN, with unconsciousness occurring within only 10-20 seconds, followed by death in convulsions within 2-3 minutes. Acute poisoning symptoms include headache, dizziness, vision disorders, pressure in chest, rapid breathing and pulse, followed by asphyxiation and unconsciousness, and clonic and tonic convulsions, and finally respiratory and cardiac arrest. Mild poisoning symptoms include headache, dizziness, hearing problems, sore throat, and visual impairment and breathing problems. The patient is fully conscious and complete recovery is possible. 3) Clinical picture of chronic hydrogen cyanide poisoning: Chronic poisoning may result from repeated effects of small doses of hydrogen cyanide (cyanides) on organism for a longer time mostly due to regular consumption of food containing cyanogenetic glycosides, or to repeated occupational exposures. Persons regularly exposed to effects of HCN have an increased red blood cells count, hypothyreosis as well as neurologically detected changes. 4) Acute toxic levels and doses: The dose–effect curve of the acute effects in humans is steep. Whereas slight effects occur at exposure to hydrogen cyanide levels of 20–40 mg/m^{3}3, 50–60 mg/m^{3}3 can be tolerated without immediate or late effects for 20 min to 1 h, 120–150 mg/m^{3}3 is dangerous to life and may lead to death after 0.5–1 h, 150 m^{3}g/m3 is likely to be fatal within 30 min, 200 mg/m^{3}3 is likely to be fatal after 10 min, and 300 mg/m^{3}3 is immediately fatal. 5) Effective and no-effect levels for chronic exposures: Workers exposed to HCN concentrations 17 mg/m^3 revealed a high prevalence of neurological, cardiovascular and gastrointestinal symptoms; after exposure to 5 – 13mg/m^3 for seven years showed in a large extent subjective symptoms (headache, weakness, ao). Thyroid enlargement has been observed in workers exposed to low concentrations in air for two years. No changes in thyroid functions (and no other biochemical or haematological deviations) were found if breathing-zone cyanide concentrations ranged between 0.01 and 3.6 mg/m^3.

	Evaluation by Competent Authorities	
Date		
Evaluation of applicant's justification		
Conclusion		
Remark:		

Section A6.12 **Annex Point IIA VI.6.9**		**MEDICAL DATA IN ANONYMOUS FORM**	
Section A6.9.12 **Annex Point IIA VI.6.9**		**Human Case Report**	
		1 REFERENCE	**Official use only**
1.1	**Reference**	Gettler AO, Baine JO. 1938. The toxicology of cyanide. Am J Med Sci 195: 182-198 (**DOC IV_27**)	
		2 GUIDELINES AND QUALITY ASSURANCE (not applicable)	
		3 MATERIALS AND METHODS	
3.1	**Substance**	Cyanides (orally), hydrogen cyanide (by inhalation)	
3.2	**Persons exposed**	Accidental poisonings, mostly found dead	
3.2.1	Sex	Information not available	
3.2.2	Age/weight	Age not available/ bw 50 – 75 kg	
3.2.3	Known Diseases	Information not available	
3.2.4	Number of persons	19	
3.2.5	Other information	Data in dogs (N=5) for comparison	
3.3	**Exposure**	Oral, by inhalation	
3.3.1	Reason of exposure	Accidental, suicidal	
3.3.2	Frequency of exposure	Single	
3.3.3	Overall time period of exposure	Information not available	
3.3.4	Duration of single exposure	Information not available for human subjects. Dogs were exposed up to death.	
3.3.5	Exposure concentration/dose	Absorbed dose calculated from concentration in organs and – for oral exposure – in GIT content.	
3.3.6	Other information		
3.4	**Examinations**	Quantitative determination of cyanide concentrations in organs at the time of death: brain, lungs, liver, kidney, heart, stomach contents and blood.	
3.5	**Treatment**	/	
3.6	**Remarks**	Testing of various analytical methods was part of the study design.	
		4 RESULTS	
4.1	**Clinical Signs**	Death or agonal coma	
4.2	**Results of examinations**	Distribution of cyanide in organs at the time of death: Concentrations (mg CN /100g tissue) varied between 0.1 and 1.4 in brain, 0.22 and 0.92 in liver and 0.3 and 2.1 in blood. The ratio of total absorbed cyanide (calculated as sum of contents in individual organs	

		and tissues) to total quantity of cyanide present in brain + liver was fairly constant, ranging between 6.2 and 8. Similar ratio was found also in dogs. Minimum lethal absorbed doses ranged between 0.5 and 1.4 mg/kg bw in human subjects, and between 1 and 1.6 mg/kg bw in dogs, both for oral and inhalation exposure.	
4.3	**Effectivity of medical treatment**	/	
4.4	**Outcome**	Death in all cases	
		5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	Cyanide concentrations in organs were determined in human subjects found dead or dying after accidental or suicidal poisoning (oral intake of cyanides or inhalation of HCN). Cyanide was measured in brain, lungs, liver, kidney, heart, stomach contents, blood and other organs and tissues. The cooled tissues were grinded and suspended in water. Distillation with airing transferred cyanide quantitatively into a series of alkali absorption tubes. $AgNO_3$ titration and colorimetric thiocyanate method proved best for quantitative detection of cyanide giving most precise results at calibration. Detection limit was 0.05 mg/kg tissue. Systematic comparison of both methods indicated very good agreement between concentrations in organ samples (**Tab.1**).	
5.2	**Results and discussion**	Concentrations of cyanide (mg CN /100g tissue) at the time of death varied between 0.1 and 1.4 in brain, 0.22 and 0.92 in liver and 0.3 and 2.1 in blood (**Tab.1**). Similar values were measured in experimental dogs exposed orally and by inhalation (**Tab. 2**): 0.5 to 1.0 and 0.4 to 1.1, respectively in brain, 0.9 to 2.5 and 0.2 to 0.5, respectively, in liver.	
5.3	**Conclusion**	Minimum lethal absorbed dose of cyanide for average adult humans has been estimated at about 50 to 60 mg (0.5 – 1.4 mg/kg bw).	

Table 1: Distribution in human organs of cyanide taken per os

Case No.	Tissue	mg. HCN / 100g $AGNO_3$ titration	mg. HCN / 100g thiocyanate method
1	Kidney	0.82	0.82
	Liver	0.72	0.73
2	Brain	0.20	0.20
	Liver	0.21	0.22
	Kidneys	0.18	0.19
	Blood	0.76	0.74
3	Liver	0.66	0.64
	Stomach contents	76.0	75.40
4	Brain	0.50	0.51
	Liver	0.34	0.33
	Lungs	0.40	0.40
	Kidneys	0.39	0.39
	Blood	0.96	1.00
5	Brain	1.59	1.56
	Lungs	1.70	1.71
	Blood	2.06	2.14
	Liver	0.90	0.92
	Kidney	0.92	0.90
	Heart	1.24	1.26
	Stomach contents	253.0	251.0
6	Brain	0.06	0.06
	Liver	0.23	0.21
	blood	0.34	0.30

Table 2: **Distribution in organs of cyanide (inhaled hydrogen cyanide in human subject and dogs 1 and 2), or taken per os (dogs 3, 4 and 5)**

	Human	Dog 1	Dog 2	Dog 3	Dog4	Dog 5
Weight (kg)……	68.3	10.3	9.10	11.90	12.7	11.30
mg HCN absorbed.....	51	16.0	10.1	16.6	14.4	12.0
mg HCN administered	(51)	(16)	(10.1)	100	20	50
Death ……	found dead	in 12 min	8 min	8 min	155min	21min
mg HCN in 100g						
Brain.....	0.32	1.08	0.41	0.50		0.43
Lungs.....	0.75	2.0	0.88	0.66		0.47
Blood.....	0.41	1.71	0.50	1.00		0.71
Liver.....	0.21	0.50	0.22	0.55		0.37
Kidney.....	0.33	1.00	0.43	0.46		0.38
Heart.....	0.42	1.23	0.50	0.32		0.24
Muscle				0.19		0.12
Stomach wall……	0.10	0.30	0.10			
GIT content (mg cyanide)	0	0	0	83.4	5.6	38.0

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Section A6.12 Annex Point IIA VI.6.9		**MEDICAL DATA IN ANONYMOUS FORM**	
Section A6.12 Annex Point IIA VI.6.9		**Human Case Report Inhalation**	
		1 REFERENCE	**Official use only**
1.1	**Reference**	J.L.Bonsall: Survival without Sequelae following Exposure to 500 mg/m^3 of hydrogen cyanide; Human toxicol. (1984), 3, 57-60 (**DOC IV_22**) Case of severe over-exposure to hydrogen cyanide	
		2 GUIDELINES AND QUALITY ASSURANCE (not applicable)	
		3 MATERIALS AND METHODS	
3.1	**Substance**	Hydrogen cyanide	
3.2	**Persons exposed**	/	
3.2.1	Sex	/	
3.2.2	Age/weight	/	
3.2.3	Known Diseases	/	
3.2.4	Number of persons	/	
3.2.5	Other information	/	
3.3	**Exposure**	Inhalation	
3.3.1	Reason of exposure		
3.3.2	Frequency of exposure		
3.3.3	Overall time period of exposure		
3.3.4	Duration of single exposure		
3.3.5	Exposure concentration/dose	Concentration of HCN in the air : 18 – 270 ppm	
3.3.6	Other information		
3.4	**Examinations**		
3.5	**Treatment**		
3.6	**Remarks**		
		4 RESULTS	
4.1	**Clinical Signs**	CN^- rapidly produces cellular anoxia by reversibly inhibiting enzymes containing ferric ions, particularly cytochrome oxidases. Death occurs from cellular asphyxia, the central nervous system being particularly sensitive. Cyanides are well absorbed through the skin and mucosae, but are most dangerous when inhaled, as they are rapidly absorbed through the bronchial mucosa and alveoli.	

4.2 Results of examinations

Physiological response to various concentration of HCN in the air:

Response	concentration (ppm)
Immediately fatal	270
Fatal after 10 min	181
Fatal after 30 min	135
Fatal after 30 - 60 min or later, or dangerous to life	110 – 135
tolerated to 30 – 60 min immediate or late effects	45 – 54
Slight symptoms after several h	18 – 30

4.3 Effectivity of medical treatment

The patient did not arrive at hospital for some 40 min followings his entry into the tank. On arrival, he was comatose, with up-going plantars and marked conjunctivitis.

Meanwhile the hospital had been alerted by the author to the possibility of cyanide poisoning. The patient was decontaminated and given intravenous sodium thiosulphate. It should be noted decontamination and treatment did not begin until approximately 1h after the first exposure. The patient subsequently began to fit and vomited. In view of the risk of inhalation of vomit, he was, therefore, paralysed, intubates and artificially ventilated. Intravenous phenytoin was given to prevent further fits. The antidote regime was repeated later, and a tracheostomy was performed.

The subsequent course was complicated by a chest infection, prolonged coma and ileus. Anti-coagulation was included in the treatment as a deep venous thrombosis developed in 1 leg.

The patient was weaned off the ventilator after 48 h, and full consciousness was regained after about 72h. He was discharged from hospital after 2 weeks. The only complication would appear to be slight loss of peripheral vision, although no baseline was available for comparison. In particular, there were no psychological changes. Unfortunately, no estimation of blood cyanide was carried out during the acute poisoning phase

A second man who briefly entered the tank, holding his breath, to fit the breathing apparatus to the unconscious man, and who was exposed for under a minute, managed to escape, but was dizzy, confused and had to be helped from the tank. He had no other symptoms, and was admitted to hospital for observation only.

4.4 Outcome

4.5 Other

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

5.2 Results and discussion

This case is unusual in that survival without sequela occurred despite exposure to HCN in the order of 500 mg/m^3 for a 6 min exposure; especially as treatment was not initiated until approximately 1h after exposure.

Even if the initial exposure was lower than 500 mg/m^3 experiments carried out subsequently have indicated that the build-up of HCN in the

	circumstances described is rapid. This report does not argue for the relaxation of standards of good industrial practice, or the threshold limit value. It does, however, illustrate that survival with minimal sequela can occur following apparently unprecedentedly high levels of HCN and that individual susceptibility to high concentrations of HCN may exist, as it does to low concentrations.	
5.3 Conclusion	The lethal dose for HCN is in the range of 0.5 – 1.5 mg/kg.	

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Section A6.13 **Annex Point IIIA VI.2**	**TOXIC EFFECTS ON LIVESTOCK AND PETS**	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ]	**Technically not feasible [ ]** **Scientifically unjustified [ ]**	
Limited exposure [x]	**Other justification**	
Justification:	With respect to the intended use, livestock and pets should not be exposed.	
References		
Undertaking of intended data submission	No studies are planned.	

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Section A6.15 Annex Point IIIA VI.4	**TOXIC EFFECT ON FOOD AND FEEDING STUFFS**	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ]	**Technically not feasible [ ]** **Scientifically unjustified [ ]**	
Limited exposure [x]	**Other justification**	
Justification:	With respect to the intended use, food and feedingstuffs should not be exposed.	
References		
Undertaking of intended data submission	No studies are planned.	

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Section A6.2 Annex Point IIA VI.6.2	**METABOLISM STUDIES IN MAMMALS. BASIC TOXICOKINETICS, INCLUDING A DERMAL ABSORPTION STUDY**	
	Information On Dermal Absorption	
Justification: **Supportive data:**	HCN absorption through skin is described in literature a number of studies, however with respect to the fact that no complete studies are available, the data found and given below are used as supporting information.	
Reference:	**1.** D.C. Walton, M.G. Witherspoon 1925. Skin absorption of certain gases. J Pharmacol Exp Ther 26: 315-324 **(DOC IV_25). Summary in DOC III_ 6.1.7a.** 2. JACC No 53, Cyanides of Hydrogen, Sodium and Potasium, and acetone Cyanohydrin (CAS No. 74-90-8, 143-33-9, 151-50-8 and 75-86-5), ECETOC JACC REPORT No. 53 European Centre for Ecotoxicology and Toxicology of Chemicals Volume I **(DOC IV_3)** 3. J.M.McNerney, M.P.H., H.H.Schrenk, PhD., 1960, The Acute Toxicity of Cyanogen, Industrial Hygiene Foundation, 4400 Fifth Avenue, Pittsburg 13, Pennsylvania, Industrial Hygiene Journal, April 1960, 121 – 124 **(DOC IV_18) Summary in DOC III_ 6.1.7c.** 4. A. Fairley, E.C.Linton, F.E.Wild , The Absorption of Hydrocyanic Acid Vapour through the Skin (with notes on other matters relating to acute cyanide poisoning), Journal of Hyg., Volume 34, October 1934, No. 3: 283 - 294 **(DOC IV_21) Summary in DOC III_ 6.1.7b.**	
Guidelines:	Not presented	
GLP:	No	
Material and methods:	Peer review	
Findings:	**Skin absorption** No study dealing with quantitative absorption of gaseous cyanides or common inorganic salts after exposure of human skin has been carried out. Evidence of the ability of cyanides and hydrogen cyanide to be absorbed through skin results from toxic effects from incidental contacts of human skin with hydrogen cyanide or cyanides. Data relating to absorption of hydrogen cyanide by animals come from studies on guinea pigs and dogs (**1**): Shaved area of abdominal skin of 8 guinea pigs has been exposed to saturated vapours of HCN. All exposed animals died at 7 -8 min; clinical symptoms of toxicity and autopsy results were the same in all animals. Dogs tolerated a concentration of 5.5 mg/l for up to 180 minutes without any ill effects. Clinical signs of toxicity (muscle twitching) appeared in animals exposed to HCN concentrations 10.9 mg/L and higher. At concentrations 11.6 mg/L and higher (concentration x time product values of 11 $g.h.m^{-3}$ and higher) 6 of 7 animals died (1 of them was euthanized). Protection of skin by hair in dogs seems to slightly enhance the tolerance. Dogs (with shaved fur on their bellies) exposed to HCN vapours showed after 30-60 minutes symptoms of toxicity including rapid breathing, muscle twitching, unconsciousness and death.	
Conclusion:	According to information available, upon absorption through skin symptoms of HCN or cyanide poisoning appear. The lethal doses are in the same range as oral LDs. The lowest LD_{50} value for dermal exposure to hydrogen cyanide was determined for female rabbits: 6.7 $mg.kg^{-1}$. The	

	reliability of the estimate is supported by all other data available. The dermal LD_{50} values for NaCN and KCN are only slightly higher (calculated as cyanide) (**2**). Permeability of abraded skin for HCN (in aqueous solution) is approx. 3 times higher than permeability of intact skin. Increased permeability should be assumed also for gaseous HCN. No data were found on dermal toxicity of gaseous HCN, but with respect to solubility of HCN the resorption proportional to time and exposed skin area should be assumed. Absorbed hydrogen cyanide is distributed within the body by blood. According to one study, up to 80% absorbed cyanides are metabolised.	

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Section A6.2 Annex Point IIA VI.6.2	**METABOLISM STUDIES IN MAMMALS. BASIC TOXICOKINETICS, INCLUDING A DERMAL ABSORPTION STUDY**	
Justification: Literature data:	Toxic kinetics, metabolism and distribution of HCN, cyanides and other sources of cyanide ion are described in literature in a number of studies. Summaries and evaluations in this section are based mostly on exhaustive and reliably peer reviewed documents: ATSDR (2004, Toxicological profile of cyanide) (**DOC IV_1**) and IPCS (2004, WHO, CICAD 61: Hydrogen cyanide and cyanides: human health aspects) (**DOC IV_5**) and Hazardous Substance Data Bank (HSDB), National Library of Medicine´s TOXNET system: Hydrogen cyanide *Peer reviewed* (**DOC IV_2**).	
References:	1. Gettler AO, Baine JO. 1938. The toxicology of cyanide. Am J Med Sci 195: 182-198 **(DOC IV_27)**. **2.** Walton DC, Witherspoon MG. 1925. Skin absorption of certain gases. J Pharmacol Exp Ther 26: 315-324 **(DOC IV_25)**. **Summary see section III_6.1.7a.** 3. Yamamoto K, Yamamoto Y, Hattori H, et al. 1982. Effects of routes of administration on the cyanide concentration distribution in the various organs of cyanide-intoxicated rats. Tohoku J Exp Med 137: 73-78 **(DOC IV_24)**. 4. BRYAN BALLANTYNE, M.D., D.Sc., Ph.D., 1983, Acute systematic toxicity of cyanides by topical application to the eye, Applied Toxicology Department, Union Carbide Corporation, P.O. Box 8361, South Charleston, West Virginia 25303 (J.Toxicol.-Cut.&Ocular Toxicol. 2(2&3),119-129) **(DOC IV_16)**. **Summary see section III_6.1.2c.** 5. J.M.McNerney, M.P.H., H.H.Schrenk, PhD., 1960, The Acute Toxicity of Cyanogen, Industrial Hygiene Foundation, 4400 Fifth Avenue, Pittsburg 13, Pennsylvania, Industrial Hygiene Journal, April 1960, 121 – 124 **(DOC IV_18)**. **Summary see section III_6.1.3a, 6.1.7c.** 6. A. Fairley, E.C.Linton, F.E.Wild , The Absorption of Hydrocyanic Acid Vapour through the Skin (with notes on other matters relating to acute cyanide poisoning), Government Experimental Establishment at Porton, Journal of Hyg., Volume 34, October 1934, No. 3 **(DOC IV_21)**. **Summary see section III_6.1.7b.** 7. Chandra H, Gupta BN, Bhargava SK, Clerk SH, Mahendre PN (1980) Chronic cyanide exposure: a biochemical and industrial hygiene study. Journal of Analytical Toxicology, 4:161–165. **(DOC IV_23)**. 8. Ansell M, Lewis FAS (1970) A review of cyanide concentrations found in human organs: A survey of literature concerning cyanide metabolism, "normal," non-fatal, and fatal body cyanide levels. Journal of Forensic Medicine, 17:148–155. **(DOC IV_28)**. 9. Schultz V, Gross R, Pasch T, Busse J, Loeschcke G (1982) Cyanide toxicity of sodium nitroprusside in therapeutic use with and without sodium thiosulfate. *Klinische Wochenschrift*, 60:1393–1400. **(DOC IV_32)**. 10. Schultz V, Bonn R, Kindler J (1979) [Kinetics of elimination of thiocyanate in 7 healthy subjects and 8 subjects with renal failure.] *Klinische Wochenschrift*, 57:243–247 (in German). **(DOC IV_34)**.	

	11. Aminlari M, Vaseghi T, Kargar MA (1994) The cyanidemetabolizing enzyme rhodanese in different parts of the respiratory systems in sheep and dog. Toxicology and Applied Pharmacology, 124:64–71. 12. Dahl AR (1989) The cyanide-metabolizing enzyme rhodanese in rat nasal respiratory and olfactory mucosa. *Toxicology Letters,* 45:199–205. 13. Sylvester DM, Holmes RK, Sander C, Way JL (1982) Interference of thiosulfate with potentiometric analysis of cyanide in blood and its elimination. *Toxicology and Applied Pharmacology*, 65:116–121. 14. Boxer GE, Rickards JC (1952) Studies on the metabolism of the carbon of cyanide and thiocyanate. *Archives of Biochemistry and Biophysics*, 36:7–26. 15. Rieders F (1971) Noxious gases and vapors. I: Carbon monoxide, cyanides, methemoglobin, and sulfhemoglobin. In: De Palma JR, ed. Drill's pharmacology in medicine, 4th ed. New York, NY, McGraw-Hill Book Company, pp. 1180–1205. 16. Tor-Agbidye J, Palmer VS, Lasarev MR, Craig AM, Blythe LL, Sabri MI, Spencer PS (1999) Bioactivation of cyanide to cyanate in sulfur amino acid deficiency: relevance to neurological disease in humans subsisting on cassava. Toxicological Sciences, 50:228–235. 17. Hartung R (1982) Cyanide and nitriles. In: Clayton GD, Clayton FE, eds. Patty's industrial hygiene and toxicology, 3rd ed. Vol. II C. New York, NY, John Wiley & Sons, pp. 4845–4906. 18. Schubert J, Brill WA (1968) Antagonism of experimental cyanide toxicity in relation to the in vivo activity of cytochrome oxidase. Journal of Pharmacology and Experimental Therapeutics, 162:352–359. 19. Lawrence WS (1947) The toxicity of sodium cyanide at slow rates of infusion. Federation Proceedings, 6(1):349. 20. Bright JE, Marrs TC (1988) Pharmacokinetics of intravenous potassium cyanide. Human Toxicology, 7:183–186. 21. Leuschner F, Neumann BW, Otto H, Möller E (1989) 13-week toxicity study of potassium cyanide administered to Sprague-Dawley rats in the drinking water. Unpublished study, Laboratory of Pharmacology and Toxicology, July [cited in JECFA, 1993]. 22. Blaschle TF, Melmon KL (1980) Antihypertensive agents and the drug therapy of hypertension. In: Goodman LS, ed. Goodman and Gilman's the pharmacological basis of therapeutics, 6th ed. New York, NY, Macmillan Publishing Co., pp. 805–806. 23. Bödigheimer K, Nowak F, Schoenborn W (1979) Pharmakokinetik und thyreotoxizität des nitroprussid-Natrium-Metaboliten Thiocyanat. Deutsche Medizinische Wochenschrift, 104:939–943.	
Absorption	**Inhalatory absorption** Cyanide as hydrogen cyanide is quickly absorbed after being inhaled (within seconds). Humans hold in their lungs 58% gaseous hydrogen cyanide at normal breathing. The following data come from exposure of dogs to a concentration of hydrogen cyanide lethal within 15 minutes and 10 minutes (1):	

1st dog ... ... absorption 16.0 mg HCN (1.55 mg/kg)
2nd dog ... ... absorption 10.1 mg HCN (1.11 mg/kg)

Oral absorption

Three dogs were administered lethal doses of hydrogen cyanide solution by gastric gavage. The quantity of absorbed cyanide was determined by the difference between supplied cyanide and cyanide that remained in stomach and intestines. The dogs were given doses of 8.4, 4.4 and 1.6mg HCN/kg, and died after 8, 21, a 155 minutes; absorption of 17, 24 and 72% of the given doses (1).

Skin absorption

No study dealing with quantitative absorption of gaseous cyanides or common inorganic salts after exposure of human skin has been carried out.
Evidence of the ability of cyanides and hydrogen cyanide to be absorbed through skin results from toxic effects from incidental contacts of human skin with hydrogen cyanide or cyanides.
In a case study, a worker carrying a new breathing apparatus was exposed to liquid hydrogen cyanide through his hand. Although inhalation of HCN was prevented, the worker fell unconscious within five minutes due to extensive absorption of liquid HCN through skin.
Absorption of gaseous HCN through dry skin is much slower: nevertheless, persons working in 20,000 ppm HCN for 8–10 minutes with protective masks are reported to experience nausea, weakness and headache.
Data relating to absorption of hydrogen cyanide by animals come from studies on guinea pigs and dogs.
Guinea pigs (with shaved fur on their bellies) exposed to saturated HCN vapours showed symptoms of toxicity including rapid breathing, muscle twitching, unconsciousness and death after 30-60 minutes. In similar tests with dogs whose bodies (shaved as well unshaved) were exposed (excluding heads) to hydrogen cyanide vapours, no symptoms of toxicity were observed for 180-minute exposure to HCN concentration of 5,572mg.m^{-3}. Exposure to HCN concentration of 15,000 mg.m^{-3} led to death after 47 minutes of dermal absorption (2).

Distribution - inhalatory exposure

Absorbed hydrogen cyanide is quickly distributed by blood into the whole body. Levels of hydrogen cyanide measured were 0.75, 0.42, 0.41, 0.33 and 0.32mg/ 100g tissue in lungs, heart, blood, kidneys and brain; the values come from a male who had died after inhalatory exposure to hydrogen cyanide. In one case of death caused by oral exposure to hydrogen cyanide, oral exposure was estimated at 30mg of CN in food approx. 3 hours before the death **(1).**

In another case, a tissue of a male who died after inhalation of hydrogen cyanide was examined with the following levels measured: 0.5mg HCN on 100ml of blood and 0.11g / 100g kidneys, 0.07mg / 100mg brain and 0.03mg/100mg liver. Cyanide level in urine was 0.2mg / 100ml and in stomach content 0.03mg/ 100g.

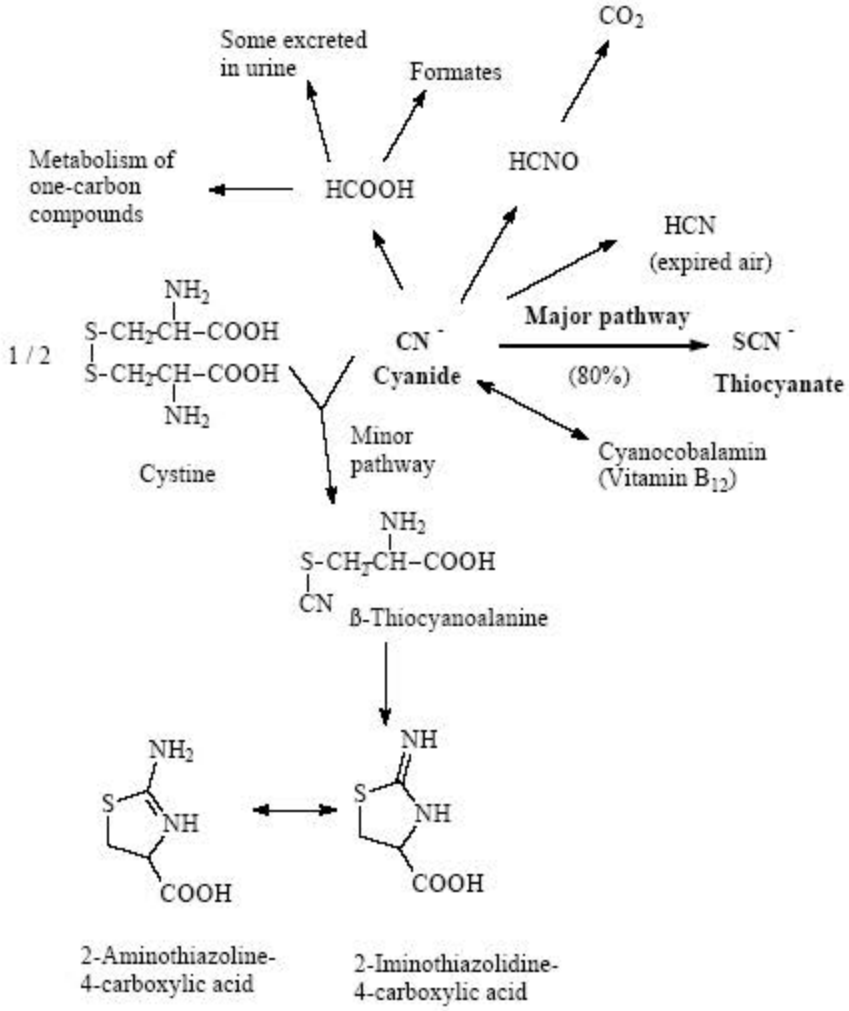
Following chronic exposure to HCN the concentration measured in the blood of smokers and non-smokers was 0.19-0.75ppm, 56.0 and 18.3µg cyanide / 100ml. Cyanide levels in control groups were 4.8µg/ml for smokers and 3.2µg/ml for non-smokers **(7).**

In rats exposed to HCN concentrations of 400 or 1,320 mg/m^3 (death after 10 or 5 minutes) no differences in cyanide concentrations in

	various body tissues, which would depend on HCN exposure concentrations, were observed. Average concentrations of cyanides in tissues in both groups of rats were 4.4µg/g of wet weight of the organ in lungs, 3.0µg/g of wet weight in blood, 2.15µg/g of wet weight in liver, 1.4µg/g of wet weight in brain, and 0.68µg/g of wet weight in spleen **(3).** In rabbits exposed to 3,040mg HCN/m^3 for 5 minutes, the following levels of cyanide content in their tissues were measured: 170µg/ 100ml blood, 48µg/ 100ml plasma, 0µg/ 100g in liver, 6µg/ 100g in kidneys, 50µg/100g in brains, 62µg/ 100g in heart, 54µg/ 100g in lungs, and 6µg/ 100g in spleen **(4).** **Distribution - oral exposure** No study of HCN distribution in a human body after oral exposure is available. In rats administered NaCN solution, CN doses 7 or 21 mg/kg bw (death after 10 or 3.3 minutes) no differences in cyanide concentrations in various body tissues, which would depend on CN dose, were observed. Average concentrations of cyanides in tissues in both groups of rats were 5.85µg/g of wet weight of the organ in lungs, 1.91 µg/ml of blood, 8.9µg/g of wet weight in liver, 1.52µg/g of wet weight in brain, and 2.1µg/g of wet weight in spleen (3). **Distribution - dermal exposure** No study of HCN distribution in a human body after dermal exposure is available. In six rabbits exposed through their skin (the skin surface is not known) to 33.75mg cyanides (in the form of HCN, approx. 5 LD50), the following levels were measured in blood and blood serum: 310 and 144µg/dl, and the following levels in tissues (in µg/100g): 26 in liver, 66 in kidneys, 97 in brain, 110 in heart, 120 in lungs, and 21 in spleen. The cyanide levels were measured immediately after the rabbits died (4).	
	Metabolism and excretion Although cyanide can interact with substances such as methaemoglobin in the bloodstream, the majority of cyanide metabolism occurs within the tissues. Cyanide is metabolized in mammalian systems by one major route and several minor routes. The major route of metabolism for hydrogen cyanide and cyanides is detoxification in the liver by the mitochondrial enzyme rhodanese, which catalyses the transfer of the sulfane sulphur of thiosulfate to the cyanide ion to form thiocyanate.(**Figure; adapted from (8)**). About 80% of cyanide is detoxified by this route. The rate-limiting step is the amount of thiosulfate. While rhodanese is present in the mitochondria of all tissues, the species and tissue distributions of rhodanese are highly variable. In general, the highest concentrations of rhodanese are found in the liver, kidney, brain, and muscle, but the supply of thiosulfate is limited **(11).** Rhodanese is present in rat nasal mucosal tissues, particularly in the olfactory region, at a 7-fold higher concentration (on a per milligram of mitochondrial protein basis) than in the liver (**12**). Dogs have a lower overall activity of rhodanese than monkeys, rats, and rabbits. A number of other sulfur transferases can also metabolize cyanide, and albumin, which carries elemental sulfur in the body in the sulfane form, can assist in the catalysis of cyanide to thiocyanate as well (**13**) . Cyanide and thiocyanate can also be metabolized by several minor routes, including the combination of cyanide with hydroxycobalamin (vitamin B12a) to yield cyanocobalamin (vitamin B12) **(14)** and the non-enzymatic combination of cyanide with cystine, forming 2-	

	iminothiazoline-4-carboxylic acid, which appears to be excreted without further change (**15) (see Figure).** In studies with rats orally administered potassium cyanide and maintained for up to 4 weeks on either a balanced diet or a diet lacking the sulfur amino acids L-cystine and L-methionine, a strongly positive linear relationship was found between blood cyanide and plasma cyanate (OCN–) concentration **(16).** It was suggested that in Africa, where there are protein-deficient populations whose levels of sulfurcontaining amino acids are low, cyanide (from prolonged use of cassava) may conceivably be converted to cyanate, which is known to cause neurodegenerative disease in humans and animals. While absorbed cyanide is principally excreted as thiocyanate in the urine, traces of free hydrogen cyanide may also be excreted unchanged in the lungs, saliva, sweat, or urine, as carbon dioxide in expired air, or as β-thiocyanoalanine in saliva and sweat **(17).** Thiocyanate was found in the urine of non-exposed people at average concentrations of 2.16 mg/litre urine for non-smokers and 3.2 mg/litre urine for smokers **(7).** Urinary excretion of thiocyanate was monitored in a man after ingestion of about 3–5 g potassium cyanide (15–25 mg cyanide/kg body weight). The results indicated that the patient excreted 237 mg of thiocyanate over a 72-h period. This quantity was substantially more than the normal average amount of thiocyanate in urine, which varies from 0.85 to 14 mg/24 h. The limiting factor in cyanide metabolism is the low concentration of the sulfur-containing substrates in the body — primarily thiosulfate, but also cystine and cysteine. The rate of spontaneous detoxification of cyanide in humans is about 1 µg/kg body weight per minute **(9),** which is considerably slower than in small rodents **(18)** or dogs (**19**). After administration of an intravenous dose of 3– 4 mg potassium cyanide to beagle dogs, blood levels decreased in a manner consistent with first-order elimination kinetics for the first 80 min. **(20).** The half-time for this phase was about 24 min, corresponding to an elimination rate constant of 0.03/min. After 80 min, the blood cyanide concentrations fell at a slower rate, with a half-time of 5.5 h. In rats, after a single oral dose, the blood elimination halftime of cyanide was 14.1 min, corresponding to a rate constant of 0.05/min. **(21)** Rats treated orally with 2 mg cyanide/kg body weight excreted 47% of the dose in the urine within 24 h. A [14C] cyanide intake study with rats (exposed to a regular intake of cyanide in the diet for 3 weeks) indicated the existence of a gastrointestinal circulation of thiocyanate, in which a substantial amount of thiocyanate, which was excreted into the stomach contents of the rat, was reabsorbed by the intestine into the body fluid, to be partly excreted in the urine and partly resecreted into the gastric contents. The relative proportion of cyanide to thiocyanate in body fluids is about 1:1000. The half-time for hydrogen cyanide elimination is about 1 h. **(8)** Half-time values of the principal metabolite thiocyanate in humans have been reported as 4 h (**22**), 2 days (**23**), and 27 days (**10**). In patients with renal insufficiency, a mean half-time of 9 days was reported. (**23**) Metabolism of cyanides includes also other sulphur transferases. Further metabolic processes of cyanides taking place in mammal organism can be seen in the following picture taken from literature **(8).**	
Distribution		
Metabolism and excretion		

Figure: Basic processes of cyanide metabolism



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Section A6.2 Annex Point IIA VI.6.2		METABOLISM STUDIES IN MAMMALS. BASIC TOXICOKINETICS, INCLUDING A DERMAL ABSORPTION STUDY	
		Information On Dermal Absorption	
		1 REFERENCE	**Official use only**
1.1	**Reference**	D.C.Walton, M.G.Witherspoon, 1925, Skin Absorption of Certain Gases, Medical Research Division, Edgewood Arsenal, Received for Publication May 15, 1925 **(DOC IV_25)**	
1.2	**Data protection**	No	
1.2.1	Data owner	/	
1.2.2	Companies with letter of access	/	
1.2.3	Criteria for data protection	No data protection claimed	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	No guidelines available	
2.2	**GLP**	No (GLP was not compulsory at the time the study was performed)	
2.3	**Deviations**	No	
		3 MATERIALS AND METHODS	
3.1	**Test material**	HCN vapours	
3.1.1	Lot/Batch number	Not reported	
3.1.2	Specification	Not reported	
3.1.2.1	**Description**		
3.1.2.2	**Purity**	97% of the liquid HCN (impurity – water in the liquid HCN)	
3.1.2.3	**Stability**	Not reported	
3.1.2.4	**Radiolabelling**	No	
3.2	**Test Animals**		
3.2.1	Species	Guinea Pig Dog	
3.2.2	Strain	Not reported	
3.2.3	Source	Not reported	
3.2.4	Sex	Not reported	
3.2.5	Age/weight at study initiation	Not reported	
3.2.6	Number of animals per group	8 guinea pigs (total number) 11 dogs (total number)	
3.2.7	Control animals	No	
3.3	**Administration/ Exposure**	Dermal Inhalation of HCN vapours excluded.	

3.3.1	Preparation of test site	Shaving of hair on the abdomen – 24 hours before the experiment Dogs were lightly morphinised 30 min before exposure	
3.3.2	Concentration of test substance	Guinea pigs: saturated vapours Dogs: 5.5 – 16.9 mg/l	
3.3.3	Specific activity of test substance		
3.3.4	Volume applied	Not relevant	
3.3.5	Size of test site	Guinea pigs: 5.06 cm^2 Dogs: whole body excl. head, abdomen shaved in all but two animals	
3.3.6	Exposure period	Guinea pigs: 7-8 minutes Dogs: 30 – 180 minutes	
3.3.7	Sampling time	Samples of air for analysis from the exposure chamber for dogs were taken in 10 min intervals.	
3.3.8	Samples		
		4 RESULTS AND DISCUSSION	
4.1	**Toxic effects, clinical signs**	**Guinea pigs** clinical symptoms – all animals, at 6 – 7 min: rapid respiration, general twitching of muscles, convulsions; death – all, at 7 – 8 min; autopsy results - all: only pink colour of lungs **Dogs** no clinical symptoms - 3 dogs (concentration 5.5 – 6.6 mg/l, exposure 30 – 180 minutes); clinical symptoms (twitching of muscles), no death –1 dog (10.9 mg/L, exposure 60 min), 1 dog (not shaved, 15.5 mg/L, 60 min) clinical symptoms, death 5 dogs (concentration 11.6 – 16.9 mg/l, exposure 47 – 105 minutes): twitching of face and throat muscles; entire body twitching; excessive salivation; slow, laboured and irregular respiration; gasping breathing; unconsciousness; absence of corneal reflex; death euthanasia - 1 dog with persisting paralysis (15.68 mg/l, 60 minutes) autopsy results - 6 dogs: pink, dry and collapsed lungs	
4.2	**Dermal irritation**	Not reported	
		5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	Non-guideline study. Shaved area of abdominal skin of 8 guinea pigs has been exposed to saturated vapours of HCN. Whole body (except head) exposure of 11 dogs to HCN vapours in concentrations of 5.5 to 16.9 mg/L air.	

5.2	**Results and discussion**	**Guinea pigs**: all exposed animals died at 7 -8 min; clinical symptoms of toxicity and autopsy results were the same in all animals. **Dogs** tolerated a concentration of 5.5 mg/l for up to 180 minutes without any ill effects. Clinical signs of toxicity (muscle twitching) appeared in animals exposed to HCN concentrations 10.9 mg/L and higher. At concentrations 11.6 mg/L and higher (concentration x time product values of 11 $g.h.m^{-3}$ and higher) 6 of 7 animals died (1 of them was euthanized). Protection of skin by hair in dogs seems to slightly enhance the tolerance. The human skin is quite unlike that of the dog (greater number of gland openings and protection of body by hair in dogs) so no unequivocal conclusions can be drawn as to the possible resistance of man to skin absorption of HCN. On the other hand, the observation that man without special protection of skin could tolerate a concentration of 11 mg/L for three hours shows that penetration through animal and human skin is of the same order.	
5.3	**Conclusion**	HCN gas passes through the uninjured skin of guinea pig and dog and can produce death of these animals at concentration x time product values of 11 $g.h.m^{-3}$ and higher.	
5.3.1	Reliability	3	
5.3.2	Deficiencies		

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Section A6.2 **Annex Point IIA VI.6.2**		**METABOLISM STUDIES IN MAMMALS. BASIC TOXICOKINETICS, INCLUDING A DERMAL ABSORPTION STUDY**	
		Information On Dermal Absorption	
		1 REFERENCE	**Official use only**
1.1	**Reference**	A. Fairley, E.C.Linton, F.E.Wild , The Absorption of Hydrocyanic Acid Vapour through the Skin (with notes on other matters relating to acute cyanide poisoning), Journal of Hyg., Volume 34, October 1934, No. 3: 283 - 294 **(DOC IV_21)**	
1.2	**Data protection**	No	
1.2.1	Data owner	/	
1.2.2	Companies with letter of access	/	
1.2.3	Criteria for data protection	No data protection claimed	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	No guidelines available	
2.2	**GLP**	No (GLP was not compulsory at the time the study was performed)	
2.3	**Deviations**	No	
		3 MATERIALS AND METHODS	
3.1	**Test material**	HCN vapour	
3.1.1	Lot/Batch number	Not reported	
3.1.2	Specification	Not reported	
3.1.2.1	**Description**	Vapours of liquid HCN	
3.1.2.2	**Purity**	Not reported	
3.1.2.3	**Stability**	Not reported	
3.1.2.4	**Radiolabelling**	No labelling	
3.2	**Test Animals**		
3.2.1	Species	Guinea pig Rabbit	
3.2.2	Strain	Not reported	
3.2.3	Source	Not reported	
3.2.4	Sex	Not reported	
3.2.5	Age/weight at study initiation	Guinea pigs: 567 – 680 g Rabbits: 1588 – 1814 g	
3.2.6	Number of animals per group	Guinea pigs: 6 (total number) Rabbits: 20 (total number)	
3.2.7	Control animals	No	