Section A6.12 **Annex Point IIA VI.6.9**	**MEDICAL DATA IN ANONYMOUS FORM**

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Findings:	Findings are summarised below in Table

Table - Summarised findings

Acute toxicity – oral (for cyanides)

Study		**Subjects**	**Dose, concentration/ exposure time**	**Effect, ED**	**Reference**
Single dose by ingestion	KNC	Human - male	Single dose	15mg/kg Respiratory effect - hyperventilation	(65)
Single dose by ingestion	KCN	Human - male	Single dose	Minimally 15mg/kg gastrointestinal vomiting and nausea	(65)
			NOAEL: 15mg/kg/day	15mg/kg blood effect	(65)

				Minimally 15mg/kg musculoskeletal system	(65)
				15mg/kg kidneys – albuminuria	(65)
Acute toxicity – dermal – systemic effects (hydrogen cyanide)					
Exposure 8-10 minutes	HCN	Human male	Exposure 8-10 minutes	Minimally 20,000ppm palpitation	(3)
Acute toxicity – inhalatory (hydrogen cyanide)					
LCLo inhalatory	HCN	Human	10 minutes	LC50 546ppm	(15)
not specified	HCN	Human - male	Not specified Fatal within 3 days	200ppm	(22)
LCLo Inhalatory	HCN	Human	60 minutes	LCLo 120mg/m^3	
Exposure 13 minutes	HCN	Human – male	13 minutes	Minimally 452ppm effects on eyes, negligible loss of peripheral vision after recovery	(69)
TCLo inhalatory	HCN	Human	TCLo 5mg/m^3 effects on behaviour, headache		
TCLo inhalatory	HCN	Human	TCLo 20mg/m^3 gastrointestinal sickness or vomiting cardiovascular pulse decrease affecting blood pressure		
LCLo inhalatory	HCN	Human 60 minutes	LCLo 100mg/m^3 circulatory changes related to brain - bleeding, thrombosis liver - changes kidneys – urogenital changes		
LCLo inhalatory	HCN	Human 30 minutes	LCLo 120 mg/m^3 circulatory changes related to brain - bleeding, thrombosis liver - changes kidneys – urogenital changes		
LCLo inhalatory	HCN	Human 10 minutes	LCLo 200mg/m^3 circulatory changes related to brain - bleeding, thrombosis liver - changes kidneys – urogenital changes		
LCLo inhalatory	HCN	Human 10 minutes	LCLo 200mg/m^3 anaesthetic effects respiration – breathlessness gastrointestinal sickness or bleeding or vomiting		

TCLo inhalatory	HCN	Human	TCLo 10ppm effects on eyes – changes in visual acuity changes in conchlear structure or function		
Acute toxicity – inhalatory – neurological effects (hydrogen cyanide)					
Exposure 13 minutes	HCN	Human - male	13 minutes	452ppm coma	(69)
Chronic toxicity – inhalatory – systemic effects (hydrogen cyanide)					
Occupational exposure not specified	HCN	Human - male	not specified	15ppm Effects: respiratory – breathlessness	(68)
				15ppm cardiovascular palpitation, chest pain	(68)
				15ppm gastrointestinal sickness	(68)
				15ppm endocrinal increased activity of thyroid gland, hormonal stimulation	(68)
Chronic toxicity – inhalatory – systemic effects (hydrogen cyanide)					
Occupational exposure not specified	HCN	Human - male	not specified	15ppm dermal effects, rash	(68)
				15ppm eye irritation	(68)
				15ppm approx. 8% loss of weight	(68)
Chronic toxicity – inhalatory – neurological effects (hydrogen cyanide**)**					
Occupational exposure not specified	HCN	Human - male	not specified	15ppm permanent headache, dizziness, paraesthaesia	(68)
Chronic toxicity – inhalatory – systemic effects (hydrogen cyanide)					
Occupational exposure not specified	HCN	Human - male	not specified	15ppm Effects: respiratory – breathlessness	(68)
				15ppm cardiovascular palpitation, chest pain	(68)
				15ppm gastrointestinal sickness	(68)

				15ppm endocrinal increased activity of thyroid gland, hormonal stimulation	(68)
				15ppm dermal effects rash	(68)
				15ppm eye irritation	(68)
Occupational exposure not specified	HCN	Human - male	not specified	15ppm approx. 8% loss of weight	(68)

Occupational and combined exposures	Cyanides are absorbed through skin and mucous membranes surface. They are hazardous and toxic when inhaled but also when the skin is exposed to the vapours. 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. A study has been elaborated based on health records of workers exposed to cyanide vapours and aerosols in factories during electrolytic galvanising and hardening. The level of cyanides was measured in the workplace, and in blood and urine of workers. Higher concentrations were found in smokers than in non-smokers. The highest exposure concentration measured was 0.8 and 0.2mg/m^3 in the breathing zone and in the main factory hall atmosphere. Tested workers complained about typical symptoms of cyanide poisoning at low concentrations (**66**) Workers exposed to HCN concentrations 4-12ppm for seven years showed in a large extent subjective symptoms including headache, weakness, changes in flavour and smell perception, nausea, oesophagus irritation, vomiting, breathing problems, lacrimation, colic, pericardial pain and nervous instability. (**1**) Thyroid enlargement may be caused by thiocyanate, the main metabolite of cyanide. This has been observed in workers exposed to low concentrations in air for two years (**2**). Thyroid enlargement has also been observed in workers exposed to cyanide salts while handling melted metals. Absorption of a cyanide dust and HCN, formed by hydrolysis of cyanide salts, was assumed. **(1)** 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 HCN through skin. Persons working in 20,000ppm HCN for 8–10 minutes with protective masks experienced nausea, weakness and headache (**3).** A chronic inhalatory occupational study describes serious neurological effects in humans (paraesthaesia – changes in sensitivity, hallucinations, headache, weakness, dizziness) and respiratory, cardiovascular effects and effects on thyroid gland at exposure to more than 6.4ppm HCN. (**67**; **4**) However, this study lacks information on the exposure level and was focused to a small group of workers. After chronic exposure to 15ppm 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. 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 **(68).**

Multiple exposures should be assumed in most occupational exposure studies.

A cross-sectional study was performed on the health effects of long-term cyanide exposure from a plating bath that contained 3% copper cyanide, 3% sodium cyanide, and 1% sodium carbonate in the electroplating sections of three factories in Egypt that employed 36 male workers (non-smokers) with 5–15 years of experience; cyanide concentrations in the breathing zones of workers (15 min averaging time) ranged from 5 to 14 mg/m^3, the averages in the three factories being 12, 7, and 9 mg/m^3 at the time of the study. There was also exposure to petrol fumes, solutions of strong soap and alkalis, and hydrochloric acid. The exposed group reported symptoms such as headache, weakness, changes in taste and smell, giddiness, irritation of the throat, vomiting, effort dyspnoea, lacrimation, salivation, and precordial pain more frequently than controls. Twenty of the exposed workers (56%) exhibited thyroid enlargement to a mild or moderate degree. None of the workers had clinical manifestations of hypo- or hyperthyroidism, but the exposed group showed a lower uptake of radiolabelled iodine in the thyroid; there was no difference in the protein-bound 131I. The exposed workers had significantly higher haemoglobin and cyanomethaemoglobin values and lymphocyte counts compared with 20 male unexposed controls. Punctate basophilia of erythrocytes was present in 28 of 36 subjects **(67)**. The contribution of the other exposures to the findings is difficult to discern.

A retrospective examination employing a questionnaire was performed with 36 former male workers (employees who could be reached and who volunteered, out of an unknown number of people actually employed) of a silver-reclaiming facility in the USA in 1983, which had been closed after the death of a worker because of cyanide poisoning. The only quantitative information on the concentrations of cyanide in the air came from a 24hour- measurement 1 day after the factory had been closed; it was 17 mg/m^3. The study revealed a high prevalence of symptoms, including eye irritation, fatigue, dizziness, headache, disturbed sleep, ringing in ears, paraesthesia of extremities, nausea, vomiting, dyspnoea, chest pain, palpitation, and weight loss (about 14% of workers reported palpitations, and 31% reported chest pain). Mild subclinical abnormalities in vitamin B12, folate, TSH levels, and thyroid function were found in silver reclaiming workers 7 months after cyanide exposure had ceased. It was noted that inhalation of hydrogen cyanide was not the only possible route of exposure of these workers in this occupational setting, as the questionnaire disclosed that more than half reported frequent direct contact with liquids containing cyanide and 22% of exposed workers were at risk of inadvertent cyanide ingestion from food and drink in the production area **(68)**.

Effects of occupational exposure (5–19 years) of 111 workers and 30 non-exposed referents to hydrogen cyanide were studied in two large case-hardening and electroplating facilities in India **(5)**. From a daily work profile and air cyanide measurements, the workers were categorized in exposure groups between 1.11 and 4.66 “cyanide-hours” (mg/m3 × h). An abnormal psychological test result overall score (composite score of “delayed memory, visual ability, visual learning, and psychomotor ability”) was observed in 31.5% of the exposed subjects, and an increase in the overall number of symptoms (headaches /heaviness in head, giddiness, lacrimation, itching of eyes, congestion of eyes, coated tongue) was found in 12.5% of the exposed workers. “Moderate” impairment in health-related scores showed an increase (no statistical analysis) at exposure levels in excess of 2.5 mg/m^3 × h in one factory and 4.35 mg/m^3 × h in the other, while findings classified as “diseased” were observed at levels in excess of 2.9 mg/m3 × h. The authors did not provide the incidences of these findings among referents or actual measurements of cyanide concentrations in the air, and few details on the carrying out of the investigations were given.

Thiocyanate, the major detoxification product of cyanide, prevents the uptake of iodine and acts as a goitrogenic agent. This effect is more pronounced in individuals with decreased capacity to excrete thiocyanate in urine due to kidney

	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

	Evaluation by Competent Authorities
Date	
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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.	

	Evaluation by Competent Authorities
Date	
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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.	

	Evaluation by Competent Authorities
Date	
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Conclusion	
Remarks	

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.	

	Evaluation by Competent Authorities
Date	
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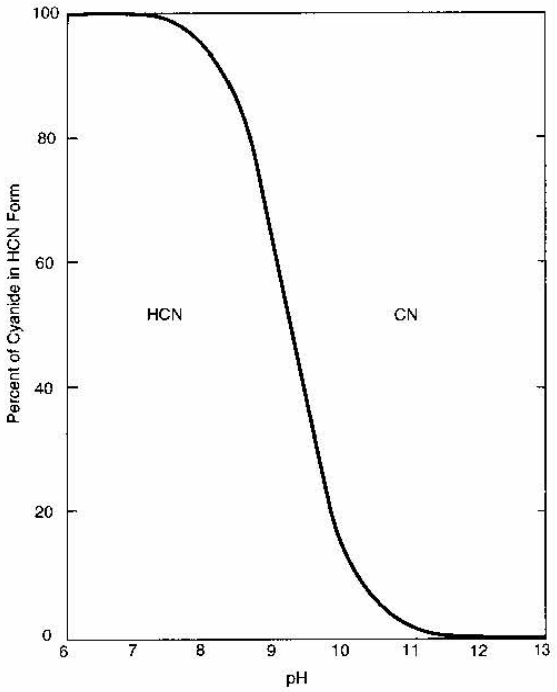
Remarks	

Section A7.1.1.1.1 Annex Point IIA VII.7.6.2.1	**Hydrolysis as a function of pH and identification of breakdown products**	
Details	Hydrolysis of hydrogen cyanide by different pH values (different concentrations of mineral acids) was published several times **(1,2,3,4).** Also was measured the rate of hydrolysis and determined the hydrolytic products, namely formamide and ammonium formate. An additional guideline study needs not to be performed, because the hydrogen cyanide hydrolysis is a well-known and characterised process. **Species in aqueous solution** Hydrolysis of hydrogen cyanide is usually expressed: $HCN + H_2O = HCONH_2$ $HCONH_2 + H_2O = HCOONH_4$ Available knowledge is summarised as follows. (All data used come from referred literature sources.	
Reference:	1. JACC No 53, Cyanides of Hydrogen, Sodium and Potassium, 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)** 2. JACC No 53, Cyanides of Hydrogen, Sodium and Potassium, 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 II **(DOC IV_4)**	
Supplement literature:	3. Krieble, V. E. and McNally, J. G.: The Hydrolysis of Hydrogen Cyanide by Acids I, *J. Am. Chem, Soc.,* 1929, 51, 3368. **(DOC IV_65)** 4. Krieble, V. E. and McNally, J. G.: The Hydrolysis of Hydrogen Cyanide by Acids II, *J. Am. Chem, Soc.,* 1933, 55, 2326. **(DOC IV_66)** 5. Krieble, V. E. and McNally, J. G.: The Hydrolysis of Hydrogen Cyanide in Acetic Acid Solutions with Mineral Acids as Catalysts, *J. Am. Chem, Soc.,* 1943, **65**, 1479. 6. Colt, A. W.; Walton, J. H.: The Reaction of Hydrogen Cyanide with Sulfuric and Phosphoric Acids, *J. Phys. Chem.*, 1937, **41**, 351. 7. Reviews of the environmental effects of pollutants. V. Cyanide. Cincinnati, OH: U. S. Environmental Protection Agency Health Effects Research Laboratory, Office of Research and Development PB289920. 8. Wiegand, G. H. and Tremelling, M.: The Kinetics and Mechanism of the Decomposition of KCN in Aqueous Alkaline Medium Hydrolysis of Simplest Nitrile, HCN, *J. Org. Chem.*, 1972, 37, 914. 9. Miyakawa, S.; Cleaves, H. J.: Implications Based on the Hydrolytic Stabilities of Hydrogen Cyanide and Formamide, *Journal of Applied Chemistry*, 2001, 196 10. Rabinovitch, B. S. and Winkler, C. A.: The Hydrolysis of Aliphatic Nitriles in Concentrated Hydrochloric Acid Solutions, *Canad. J. Res,* 1942. 20B, 221–230. 11. Marsh, J. D. F. and Martin, M. J.: The Hydrolysis and Polymerization of Hydrogen Cyanide in Alkaline Solutions, *J. Appl. Chem.* 1957, 7, 205–209. 12. Sanchez, R. A.; Ferris, J. P. and Orgel, L. E.: Studies in Prebiotic Synthesis II. Synthesis of Purine Precursors and Amino Acids from Aqueous Hydrogen Cyanide, *J.Mol. Biol.* 1967, 30, 223–253. 13. Tan, T. C. and Teo, W. K.: Destruction of Cyanides by Thermal Hydrolysis, *Plat. and Surf. Fin.* 1987, 74 (4), 70–73.	

14. Hine, J.; King, R. S.-M.; Midden, W. R. and Sinha, A.: Hydrolysis of Formamide at 80°C and pH 1–9, *J. Org. Chem.* 1981, 46, 3186–3189.
15. Mittal, S.; Gupta, K. S. and Gupta, Y. K.: Kinetics of Carboxylic Acid Catalysed Hydrolysis of Formamide: Evidence for Specific Hydronium Ion Catalysis, *Indian J. Chem,* 1981, 20A, 1220–1221.
16. Mittal, S.; Gupta, K. S. and Gupta, Y. K.: Kinetics & Mechanism of Acid Hydrolysis of Formamide, Acetamide, Propanamide & Butanamide over an Extended Concentration Range: Kinetic Evidence for Fast Protonation Pre-equilibrium, *Indian J. Chem.,* 1982. 21A, 357–360.
17. Skundric, B. and Penavin, J.: Acid Catalysed Amide Hydrolysis in Water-Ethanol Mixtures. Medium Interactions Study, *Zeitschrift Physikalische Chemie Neue Folge* 1984, 141, 29-31.

The percentage of CN^- ion in HCN form in dependence on pH is shown in Fig. 1.



In water, hydrogen cyanide and cyanide ion exist in equilibrium with their relative concentrations primarily dependent on pH and temperature **(5)**.
Apparently at pH < 8.3 the HCN is the dominant species, at pH < 7 99% will be as HCN molecule, and at pH > 10 the CN^- is the dominant ion.

From the studies **(6,7)** it is also evident that hydrolysis of HCN depends on acid concentration and temperature, with the raising temperature also increased (comparing **Fig. 2** and **Fig.3**).
In both cases the hydrolysis increased with an increase in the acid concentration at the same temperature, and it is also dependent by the same concentration of acid on the strength of a selected mineral acid, **Fig. 4**.

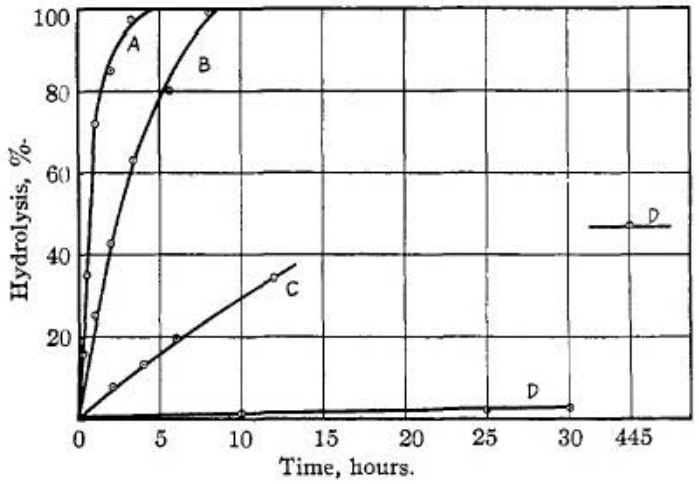


Fig. 2
The hydrolysis of HCN at 45°C, curve: **A** – 7.84 *N* HCl, **B** – 5.88 *N* HCl, **C** – 3.92 *N* HCl, **D** – 1.95 *N* HCl

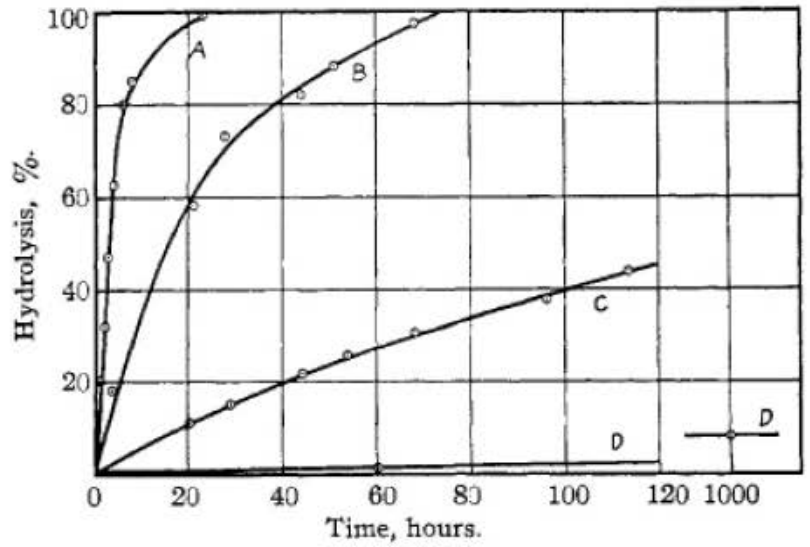


Fig. 3
The hydrolysis of HCN at 30°C, curve: **A** – 7.84 *N* HCl, **B** – 5.88 *N* HCl, **C** – 3.92 *N* HCl, **D** – 1.95 *N* HCl

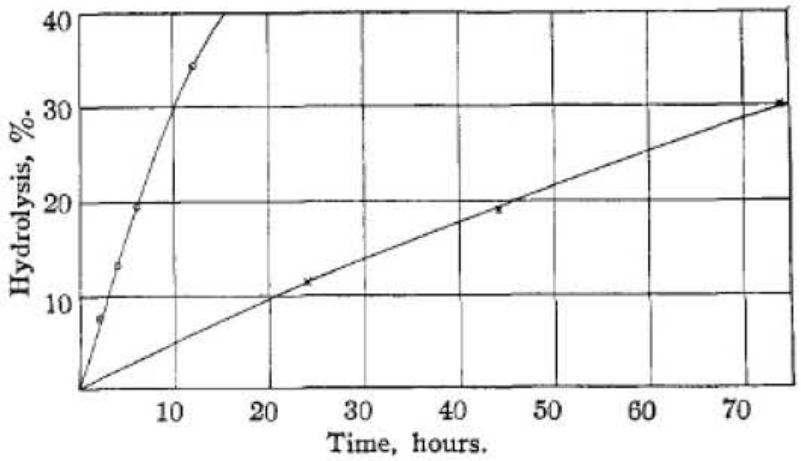


Fig. 4
O – 0.4 *N*HCl at 45°C, **X** – 4*N*HBr at 45°C

Hydrolyses of HCN and formamide are expressed

$$HCN \xrightarrow[k_1^{HCN}]{H_2O} HCONH_2 \xrightarrow[k_1^{formamide}]{H_2O} HCOOH + NH_3$$

where k_1^{HCN} and $k1^{formamide}$ are the pseudo first-order rate constants for the hydrolysis of HCN and formamide, respectively.
The rates are

$$-\frac{d[HCN]}{dt} = k_1^{HCN}[\Sigma HCN]$$

$$-\frac{d[HCONH_2]}{dt} = k_1^{formamide}[HCONH_2]$$

where $\sum$ HCN = HCN + CN−. The pH rates profiles of HCN and formamide hydrolyse are shown in **Figures 5 and 6**, respectively. The kinetic data are available on a website: (http://members.aol.com/smiyakawa/shin/science/hydrolysis/kinetic.html) or upon request. The hydrolyses of HCN and formamide are catalysed by acid and base **(6).**

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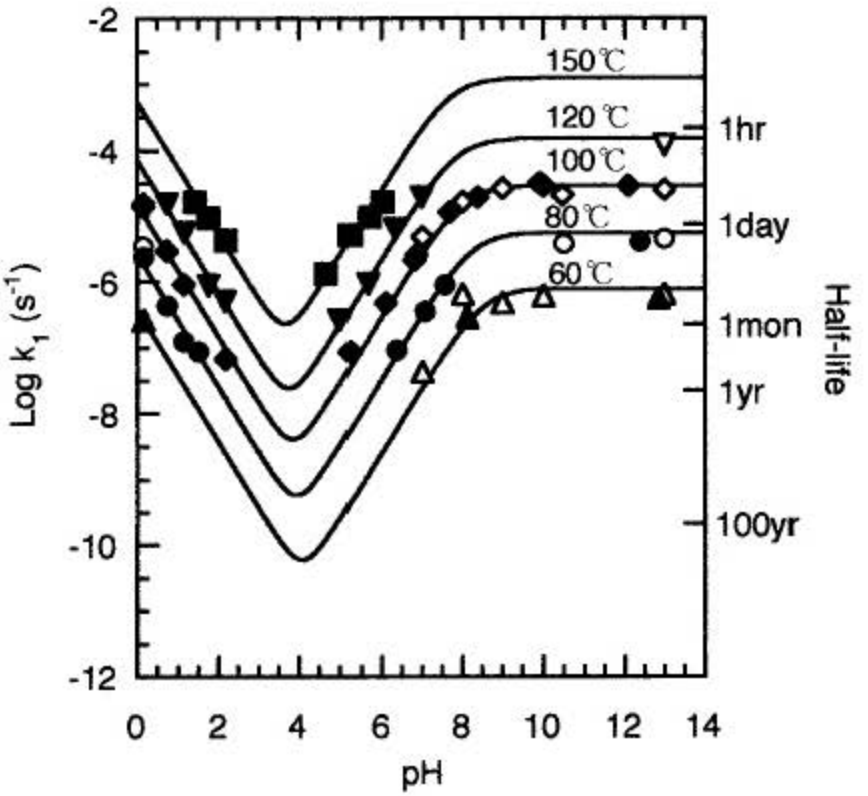

Fig. 5
The pH rate profile for the hydrolysis of HCN. Reference data (**7,8,9,10,11**)

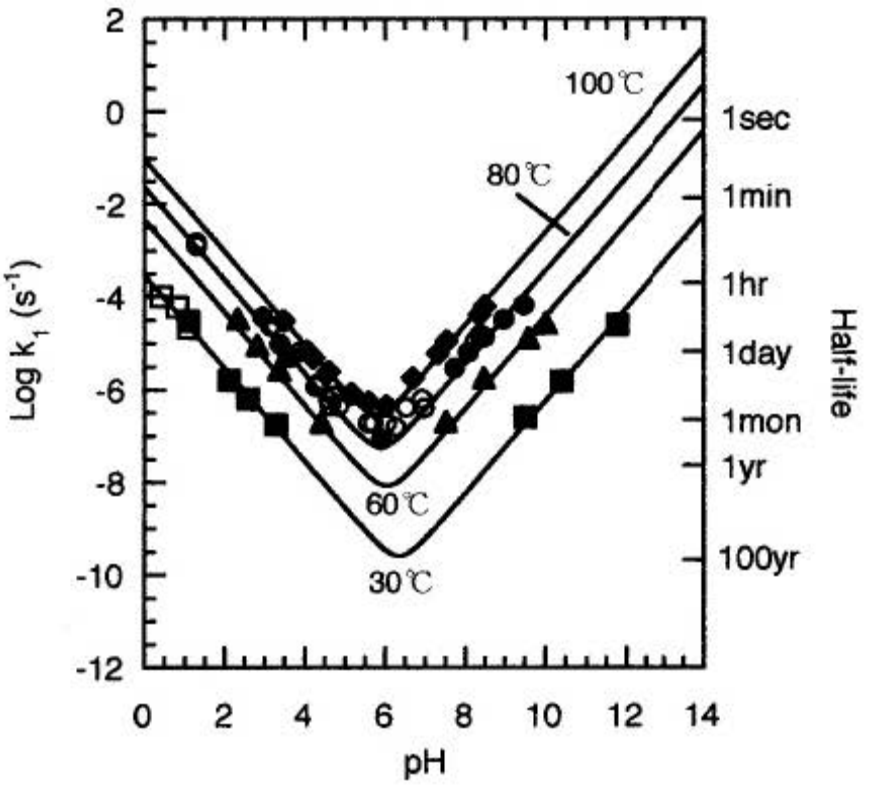

Fig. 6
The pH rate profile for the hydrolysis of formamide. Reference data (**7,12,13,14,15,16,17**).

By extrapolation of results, see **fig. 5** The pH rate profile for the hydrolysis of HCN, it was estimated that the half-life of HCN at 20 °C and pH around 7 will be approximately 1 year or longer.

The estimation is evidenced also by the graph of the HCN degradation depending on pH HCl (**fig. 3**), when HCN at 30 °C and HCl concentration 1.95 N practically does not degrade.

According to the evaluative criteria of method C.7 - Degradation - Abiotic Degradation Hydrolysis as a Function of pH, Council Regulation (EC) No. 440/2008, Published in O.J. L 142, 2008, a substance with a half-life of 1 year may be considered hydrolytically stable.

Conclusion:

The hydrolysis rate of HCN is very low.

Undertaking of intended data submission

No studies are planned.

	Evaluation by Competent Authorities
Date	
Evaluation of applicant's justification	
Conclusion	
Remarks	

Section A7.1.1.1.2 **Annex Point IIA VII.7.6.2.2**	**Phototransformation in water including identity of the products of transformation**	
References:	**1.** D. J. Lary, Atmospheric pseudohalogen chemistry, Atmos. Chem. Phys. Discuss., 4, 5381–5405, 2004 www.atmos-chem-phys.org/acpd/4/5381/ SRef-ID: 1680-7375/acpd/2004-4-5381 © European Geosciences Union 2004 **(DOC IV_67)** **2.** JACC No 53, Cyanides of Hydrogen, Sodium and Potassium, 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.** JACC No 53, Cyanides of Hydrogen, Sodium and Potassium, 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 II **(DOC IV_4)** **4.** S. N. Frank and A. J. Bard, "Heterogeneous Photocatalytic Oxidation of Cyanide Ion in Aqueous Solutions at TiO2 Powder," *J. Am. Chem. Soc.*, *99*, 303 (1977).	
Detailed justification:	The influence of light on hydrogen cyanide in solution in water was investigated several times **(1, 2)**. There is no need to perform an additional guideline study as the process is well known and characterised. Hydrogen cyanide is a monomer and is inhibited with sulphuric, phosphoric or glycolic acid to prevent polymerization. Hydrogen cyanide is miscible in water. HCN is highly volatile (vapour pressure of 84 kPa at 20 °C) and can volatilize from water into the atmosphere. Airborne HCN undergoes slow photolysis, but the major part is absorbed into the oceans, where cyanide is removed by chemical and/or biological degradation. The overall atmospheric lifetime of HCN is 5 to 6 months **(2).** At pH less than 9.2, most of the free cyanide in water will exist as hydrogen cyanide. Cyanide can react in water with metals typically present (e.g. K, Na, Fe) to form complexes. Some of these complexes, such as iron and copper cyanide, are very stable and others, such as zinc cyanide, decompose quite readily. Photocatalytic degradation using UV-irradiated TiO_2 suspension has been investigated for destroying both free and complex cyanide **(3)**. The TiO_2 film has a high refraction ratio and when it is irradiated by UV light, less than 385 nm, the band gap energy is exceeded. There are created hydroxyl radicals as very reactive molecules and cyanides are oxidized to CO_2 or H_2O primarily. Under the best conditions, TiO_2–SiO_2 photo catalyst, of a specific surface area of 850 m^2/g, resulted in cyanide removal efficiency of 98.74%. Photo-catalytic oxidation (PCO-technology) kills and decomposes addressing volatile organic compounds (HCN) or odours. There are many methods used in reducing the toxicity of air and water. The main advantage of the photo degradation of pollutants in water is their total mineralization to simple, non-toxic products e.g. CO_2 and water. Titanium dioxide, mainly in its anatase crystalline form, non-toxic character, photo stability and biological and chemical inertness was found as an almost ideal photo catalyst but cannot be induced via the visible light. Comparison of the efficiency of photo catalytic decomposition of different TiO_2 forms with no catalytic process shows **Fig 1**.	

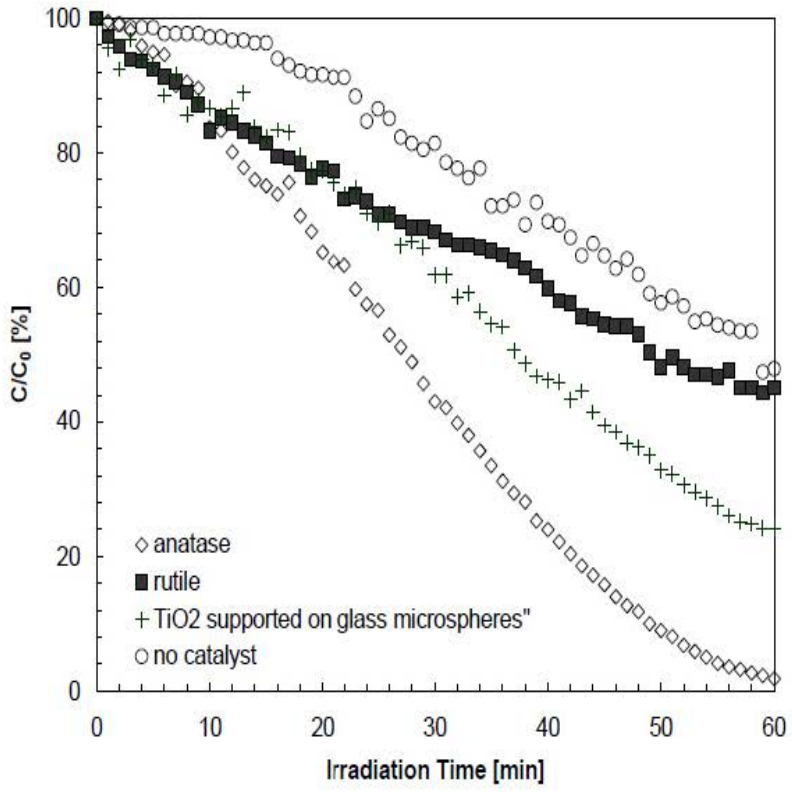

Fig. 1. Impact of catalyst type on elimination of free cyanides from aqueous solution at pH 12

The results suggest that commercial anatase and anatase supported on glass hollow microspheres are the most effective catalysts for photo catalytic degradation of free cyanide.

Recently the supported TiO_2 e.g. titanium-silica systems in the form of aerogels have been suggested to be more active than the pure titanium catalysts. In those aerogels silica provides an excellent porous structure with an extremely high surfaced area and porosity, allowing good adsorption of pollutants.

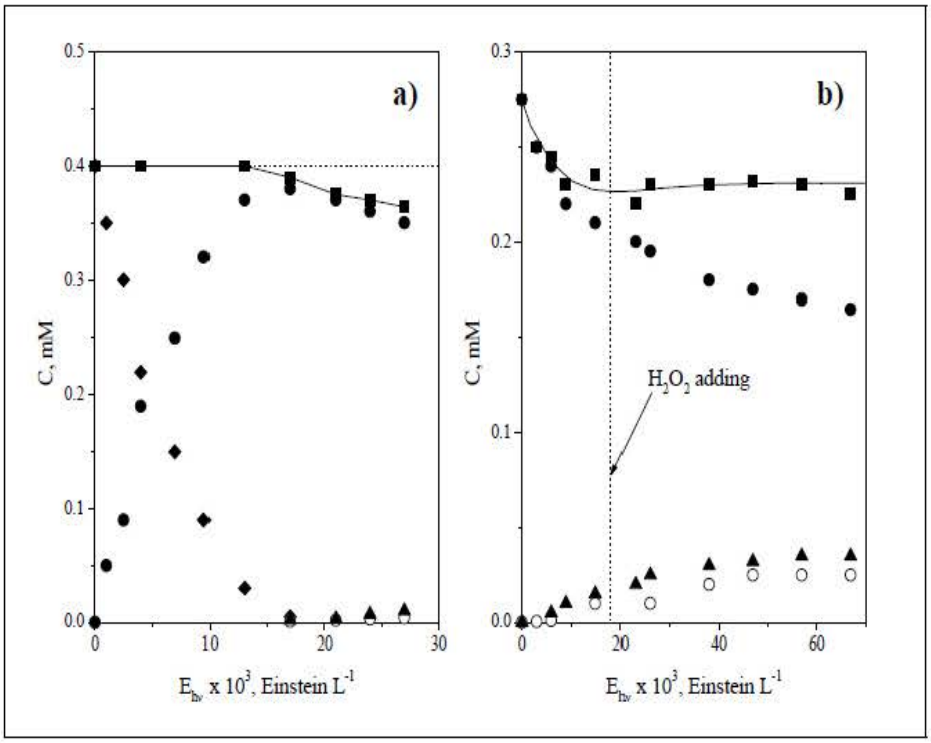

Fig. 2. (a) Typical cyanide degradation test with a catalyst amount of 0.2 g/L.

(b) Cyanate degradation adding hydrogen peroxide after certain time.

Concentrations of cyanide(♦), cyanate(●), nitrite (▲), nitrate (o), and nitrogen balance (■) versus the cumulative photonic energy, E_{hv}.

For a typical run carried out with a catalyst amount of 0.2 g/L (TiO_2),(**Figure 2a**) reports the experimental values of cyanide, cyanate, nitrite and nitrate concentrations versus E_{hv}. In this Figure the nitrogen mass balance is also reported. It can be observed that the balance is satisfied during the course of cyanide photo-oxidation but it is not satisfied during the subsequent cyanate photo-oxidation. In order to better understand this behaviour, which was shown by all the runs, some runs were carried out using cyanate as the starting reagent and by adding hydrogen peroxide to the system during the occurrence of the photoreaction.

For a representative run (**Figure 2b**) reports the experimental results of cyanate concentration versus E_{hv}. It can be noticed that the nitrogen molar balance is closed only after the addition of hydrogen peroxide to the reacting system. The CPC photo reactivity results indicate that cyanate ion is the first photo-oxidation product of cyanide; the subsequent cyanate photo oxidation eventually determines the formation of nitrite and nitrate ions whose amounts, however, denote a lacking of nitrogen mass balance in the course of the reaction. The addition of H_2O_2 to the reacting system determines the closure of nitrogen mass balance even if the photo-oxidation rate of CNO- does not significantly change in the presence of H_2O_2.

Limited exposure [ ]	**Other justification [ ]**	
Undertaking of intended data submission	No studies are planned.	

	Evaluation by Competent Authorities
Date	
Evaluation of applicant's justification	
Conclusion	
Remarks	