Section A6.1 **Annex Point IIA VI.6.1**		**ACUTE TOXICITY**	
Section A6.1.2 **Annex Point IIA VI.6.1.2**		**Acute Percutaneous Toxicity**	
		1 REFERENCE	**Official use only**
1.1	**Reference**	Bryan Ballantyne, 1988, Toxicology and Hazard Evaluation of Cyanide Fumigation Powders, Applied Toxicology Department, Union Carbide Corporation, Danbury, Connecticut 06817, Clinical Toxicology, 26 (5&6), 325-335 Copyright © 1988 by Marcel Dekker, Inc.; **(DOC IV_14)**	
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;(methods used comparable to guideline of Acute Dermal Toxicity)	
2.2	**GLP**	Not reported	
2.3	**Deviations**	No	
		3 MATERIALS AND METHODS	
3.1	**Test material**	NaCN powder	
3.1.1	Lot/Batch number	Not reported	
3.1.2	Specification	Pure NaCN	
3.1.2.1	**Description**	Powder	
3.1.2.2	**Purity**	Pure	
3.1.2.3	**Stability**	Not reported	
3.2	**Test Animals**		
3.2.1	Species	Rabbit	
3.2.2	Strain	Rabbit – New Zealand white	
3.2.3	Source	Not reported	
3.2.4	Sex	Females only	
3.2.5	Age/weight at study initiation	Rabbits: 2200 - 2600 g	
3.2.6	Number of animals per group	6-12 animals/dose (3 groups of rabbits: 1.with exposure on dry skin, 2.with exposure on moist skin and 3.with exposure on abraded skin)	
3.2.7	Control animals	Not reported	

3.3	**Administration/ Exposure**	Dry, moist or abraded skin	
3.3.1	Post exposure period	Not reported	
3.3.2	Area covered	Clipped dorsal trunk skin (% of body surface – not reported)	
3.3.3	Occlusion	Occlusive contact (polyethylene sheeting held in place with bandaging tape)	
3.3.4	Vehicle	No (only powdered NaCN was applied)	
3.3.5	Concentration in vehicle	N/A	
3.3.6	Total volume applied	Dose range Dry skin: 200 mg/kg bw Moist skin: 7 – 20 mg/kg bw Abraded skin: 5 – 10 mg/kg bw	
3.3.7	Duration of exposure	6 hours	
3.3.8	Removal of test substance	Not reported	
3.3.9	Controls	Not reported	
3.4	**Examinations**	Clinical observations (signs of toxic effects, the time of onset of signs, time of death), examination of eyes (Necropsy and other exam. – not reported)	
3.5	**Method of determination of LD_{50}**	LD_{50} was computed from the dose-mortality data by probit analysis using a Fortran computer program (LD_{50} with 95% confidence limits and slopes of regression lines).	
3.6	**Further remarks**		
		4 RESULTS AND DISCUSSION	
4.1	**Clinical signs**	Time to first signs/Time to death: dry skin: no signs/ no death moist skin: 9.0 – 145.0 minutes/ 21.0 – 170. 0 minutes abraded skin: 5.0 – 110.0 minutes/ 12.0 – 180. 0 minutes Clinical signs: rapid breathing, weak movements, tremors, respiratory distress, severe spasms, convulsions, irregular shallow breathing, coma.	
4.2	**Pathology**	Not reported	
4.3	**Other**		
4.4	**LD_{50}**	Percutaneous dry skin: >200 mg/kg moist skin: 11.8 mg/kg abraded skin: 7.7 mg/kg	

		5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	Non-guideline study; the test substance (NaCN powder) was applied on clipped dry, moist or abraded skin and held in occluded contact for 6 hours - several groups of unstarved rabbits with various dose levels. Following exposure animals were observed for signs of toxic effects and the times of onset of signs and times to death were noted. Survivors were kept only for 7 days (according to the Guidelines observation period after exposure is 14 days). Body weights of animals were recorded only at the beginning of the study.	
5.2	**Results and discussion**	Applied to dry intact skin NaCN did not produce systemic toxicity. However, on moistened intact skin or abraded skin lethal amounts of cyanide were absorbed. Time to first signs and time of death were shorter in animals with the abraded skin than moistened skin Study was conducted to assess potential handling hazards from pesticidal use of powdered NaCN. On coming into contact with water NaCN powder liberates HCN vapour - it can evolve 20% (by weight) of HCN.	
5.3	**Conclusion**	Percutaneous LD_{50} dry skin: >200 mg/kg moist skin: 11.8 mg/kg abraded skin: 7.7 mg/kg	
5.3.1	Reliability	2	
5.3.2	Deficiencies	The study from 1988 is not in the GLP system, but the method used is comparable to methods standardised by EU directive 440/2008	

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Section A6.1 Annex Point IIA VI.6.1		**ACUTE TOXICITY**	
Section A6.1.2 Annex Point IIA VI.6.1.2		**Acute Eye Toxicity**	
		1 REFERENCE	**Official use only**
1.1	**Reference**	Bryan Ballantyne, 1988, Toxicology and Hazard Evaluation of Cyanide Fumigation Powders, Applied Toxicology Department, Union Carbide Corporation, Danbury, Connecticut 06817, Clinical Toxicology, 26 (5&6), 325-335 ;Copyright © 1988 by Marcel Dekker, Inc. **(DOC IV_14)**	
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 for this route of exposure (for systemic toxicity testing).	
2.2	**GLP**	No	
2.3	**Deviations**	No guideline available	
		3 MATERIALS AND METHODS	
3.1	**Test material**	**NaCN powder**	
3.1.1	Lot/Batch number	Not reported	
3.1.2	Specification	Pure NaCN	
3.1.2.1	Description	Powder	
3.1.2.2	Purity	Pure	
3.1.2.3	Stability	Not reported	
3.2	**Test Animals**		
3.2.1	Species	Rabbit	
3.2.2	Strain	Rabbit – New Zealand white	
3.2.3	Source	Not reported	
3.2.4	Sex	Females only	
3.2.5	Age/weight at study initiation	Rabbits: 1900.0 – 2200.0 g	
3.2.6	Number of animals per group	10 animals/each dose	
3.2.7	Control animals	Not reported	
3.3	**Administration/ Exposure**	ocular, dermal (dry, moist or abraded skin)	
3.3.1	Post exposure period	7 days	

3.3.2	Vehicle	No (only powdered NaCN was applied)	
3.3.3	Concentration in vehicle	Dose range 3.18 – 9.96 mg/kg bw	
3.3.4	Total volume applied	/	
3.3.5	Controls	Not reported	
3.4	**Examinations**	Clinical observations (signs of toxic effects, the time of onset of signs, time of death), examination of eyes (Necropsy and other exam. – not reported)	
3.5	**Method of determination of LD_{50}**	LD_{50} was computed from the dose-mortality data by probit analysis using a Fortran computer program (LD_{50} with 95% confidence limits and slopes of regression lines).	
3.6	**Further remarks**		
		4 RESULTS AND DISCUSSION	
4.1	**Clinical signs**	Time to first signs/ Time to death: unstarved rabbits: 2.0 – 7.0 minutes/ 2.0 – 12.0 minutes Clinical signs: rapid breathing, weak movements, tremors, respiratory distress, severe spasms, convulsions, irregular shallow breathing, coma.	
4.2	**Pathology**	Not reported	
4.3	**Other**	Local signs of irritation after ocular exposure: lacrimation, moderate conjunctival hyperaemia, mild chemosis; in survivors – more severe conjunctival hyperaemia, moderate corneal opacification and mild iritis after 24 hours; mild conjunctival inflammation and mild to moderate keratitis after 7 days.	
4.4	**LD_{50}**	Eye- unstarved rabbits: 4.5 mg/kg	
		5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	Non-guideline study; the test substance (NaCN powder) was applied into the inferior conjunctival sac of one eye of unstarved rabbits – several groups with various dose levels. Following exposure animals were observed for signs of toxic effects and the times of onset of signs and times to death were noted. Survivors were kept only for 7 days (according to the Guidelines observation period after exposure is 14 days). Body weights of animals were recorded only at the beginning of the study.	
5.2	**Results and discussion**	Lethal systemic toxicity was produced by contamination of rabbit eye with NaCN powder, which also caused a rapid onset of moderately severe conjunctivitis and keratitis Study was conducted to assess potential handling hazards from pesticidal use of powdered NaCN. On coming into contact with water NaCN powder liberates HCN vapour - it can evolve 20% (by weight) of HCN.	
5.3	**Conclusion**	Ocular LD_{50} of NaCN powder in unstarved rabbits: 4.5 mg/kg bw	
5.3.1	Reliability	2	
5.3.2	Deficiencies	The study from 1988 is not in the GLP system.	

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Section A6.1 Annex Point IIA VI.6.1		**ACUTE TOXICITY**	
Section A6.1.2 Annex Point IIA VI.6.1.2		**Acute systemic toxicity by topical application to the eye**	
		1 REFERENCE	**Official use only**
1.1	**Reference**	BRYAN BALLANTYNE, M.D., D.Sc., Ph.D., 1983, Acute systemic 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)**	
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	
2.3	**Deviations**	The study from 1983 is not in the GLP system.	
		3 MATERIALS AND METHODS	
3.1	**Test material**	Hydrogen cyanide	
3.1.1	Lot/Batch number	Not stated	
3.1.2	Specification		
3.1.2.1	**Description**		
3.1.2.2	**Purity**	Not stated	
3.1.2.3	**Stability**	Not stated	
3.2	**Test Animals**		
3.2.1	Species	Rabbits	
3.2.2	Strain	Not stated	
3.2.3	Source	Not stated	
3.2.4	Sex	Female	
3.2.5	Age/weight at study initiation	Adult/ average weight 1.99 kg (S.D. ± 0.34 kg; range 1.3 to 2.78 kg)	
3.2.6	Number of animals per group	10 animals in each group	
3.2.7	Control animals	Not stated	

3.3	**Administration/ Exposure**	Ocular	
3.3.1	Vehicle	Water	
3.3.2	Concentration in vehicle	Concentrations (w/v) of cyanide in the solution were 3.13% - 3.97% HCN	
3.3.3	Total volume applied	Constant dose-volume of 0.03 ml/kg was used in all cases. Resulting dose = 0.94 – 1.19 mg/kg bw	
3.3.4	Controls		
3.4	**Examinations**	Clinical observations, necropsy, haematology	
3.5	**Method of determination of LD_{50}**		
3.6	**Further remarks**		
		4 RESULTS AND DISCUSSION	
4.1	**Clinical signs**	Tight blepharospasm;, rapid panting breathing; weak and ataxic movements; convulsions; tonic spasms; loss of consciousness; irregular, shallow and gasping breathing; cessation of breathing and death (average 2.5 min.). The times for these sign to appear were 30-60 and 45-90 sec. Sign of toxicity were seen at the following and higher dosage: 0.94 mg/kg. Rapid shallow breathing, the first sign of toxicity, appeared more quickly with solutions of HCN but was present in all animals by 2.5 min.	
4.2	**Pathology**	Congestion of the lung and kidneys and presence of multiple scattered subpleural and epicardial petechiae.	
4.3	**Other**	Cyanide concentrations (µg/100g of wet tissue)±S.E. for dosage of 5.25 mg CN/kg: 6 animals per group Heart.....205±28 µg/100g Lung.....224±51 µg/100g Brain.....107±15 µg/100g Spinal Cord.....29±8 µg/100g Liver.....15±8 µg/100g Kidney.....14±10 µg/100g Whole blood.....552±51 µg/dl Serum.....341±53 µg/dl S.E. = standard error of the mean Concentrations were measured in adult female albino rabbits of average weight 2.24 kg(S.D. ±0.24; range 1.9 – 2.8 kg)	
4.4	**LD_{50}**	1.04 mg/kg (0.96 – 1.13) ; 0.039 (0.36 – 0.042) mmol/kg with 95% confidence limits	
		5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	The acute toxicity of hydrogen cyanide by topical application to the eye	

5.2	**Results and discussion**	Using the rabbits, the LD_{50} values (with 95% confidence limits), in mmol/kg, with aqueous solutions instilled into the inferior conjunctival sac were determined to be 0.039 (0.036-0.042) for HCN. Sign of toxicity appeared rapidly and death occurred within 3 to 12 min of the eye being contaminated.	
5.3	**Conclusion**	Contamination of the eye with hydrogen cyanide solution could be hazardous: for this route of exposure. LD_{50} is about 1 mg/kg bw.	
5.3.1	Reliability	3	
5.3.2	Deficiencies	The study from 1983 is not in the GLP system. No serious deficiencies.	

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Section A6.1 Annex Point IIA VI.6.1	**ACUTE TOXICITY**	

Section A6.1.3 Annex Point IIA VI.6.1.3	**Acute Inhalation Toxicity**	
Justification: **Supportive data:**	The active substance hydrogen cyanide is a gas at body temperature. Hydrogen cyanide is known to be a highly toxic substance by inhalatory exposure for humans and for all species of laboratory organisms. The mechanism of its toxic action is well known. Although literature provides a large number of data, no single study meets requirements for a key study. 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. Ballantyne B. 1983a. The influence of exposure route and species on the acute lethal toxicity and tissue concentrations of cyanide. In: Hayes AW, Schnell RC, Miya TS, eds. Developments in the science and practice of toxicology. New York, NY: Elsevier Science Publishers, 583-586 **(DOC IV_15);** 2. AMRL. 1971. The acute toxicity of brief exposures to hydrogen fluoride, hydrogen chloride, nitrogen dioxide, and hydrogen cyanide singly and in combination with carbon monoxide. Wright-Patterson Air Force Base, OH: Aerospace Medical Research Laboratory. AD751442 3. Hume AS, Mozigo JR, McIntyre B, et al. 1995. Antidotal efficacy of alpha-ketoglutaric acid and sodium thiosulfate in cyanide poisoning. Clin Toxicol 33(6):721-724. 4. Matijak-Schaper M, Alarie Y. 1982. Toxicity of carbon monoxide, hydrogen cyanide and low oxygen. J Combust Toxicol 9:21-61. (**DOC IV_17);** 5. Fundamental and Applied Toxicology. (Academic Press, Inc., 1 E. First St., Duluth, MN 55802) V.1-40, 1981-97. For publisher information, see TOSCF2 v. 9, p. 236, 1987 (FAATDF) 6. Toxicology and Applied Pharmacology. (Academic Press, Inc., 1 E. First St., Duluth, MN 55802) V.1- 1959- v. 42, p. 417, 1977 (TXAPA9); 7. Arvind K. Chaturvedi, Boyd R. Endecott, Roxane M. Ritter, Donald C. Sanders Variations in Time-to-Incapacitation and Blood Cynanide Values for Rats Exposed to Two Hydrogen Cyanide Gas Concentrations, Washington, D.C. 20591 8. Monsanto Co.Report 1985. One-month inhalation toxicity of acetone cyanohydrin in male and female Sprague-Dawley rats. St Louis, Monsato Co. Report ML-81-178/810068 (US EPA/OPTS Public Files No. 878216393). 9. 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; summarised in section 6.1.3a. **(DOC IV_18)** 10. The Merck Index -An Encyclopedia of Chemicals, Drugs, and Biologicals. Whitehouse´Station, NJ: Merck and Co., Inc., 2006., p. 830] **PEER REVIEWED**	
Guidelines:	Not presented.	
GLP:	No. All studies before GLP requested.	
Material and methods:	Inhalation exposures to HCN or acetone cyanohydrin; time vs. concentration exposures of rats, mice, guinea pigs, rabbits, dogs, goats and monkeys. A general	

	toxicity and lethality measure, classical LC_{50} calculations, estimates of lethal doses.
Results and discussion:	Relative sensitivity to HCN vapours has been tested in various species, from mice to monkeys (mice, rats, guinea pigs, rabbits, cats, dogs, goats and monkeys); time to death of half animals exposed to a concentration of 1000 mg/m^3 varied between 1.0 and 3.5 minutes, values (i.e., resistance) increased with body mass (***Barcroft 1931, this study is not included in the list of references***). The range of sensitivity values corresponds to the range of minute respiratory volumes per kg body weight, indicating that the received LD_{50} dose (per kg bw) was similar across species. Inhalation LC_{50} values in rats ranged from 158 mg/m^3 for a 60 minute exposure to 3,778 mg/m^3 for exposure time 10 sec - see **Table 2**. These LC values correspond to total doses inhaled: 0.16mg/kg bw for 10 second exposure and 2.36 mg/kg bw for 60 min. exposure. For longer exposures, the LC50 values seem not to decrease markedly, perhaps as a result of balanced resorption and elimination of CN ions. LC_{50} values interpolated from rat data for exposure times 5 to 30 minutes are similar to fatal concentrations from case reports in humans (100 – 300 mg/m^3, exposure times 30 to 5 minutes). Exposure of rats (Sprague-Dawley) to acetone cyanohydrin for 6 hours in an airborne concentration of 225 mg/m^3(equivalent to 71 mg/m^3 of hydrogen cyanide) resulted in the death of 3/10 males but none of 10 females. Similar values were found in other animal species and in other studies, as summarised below in **Table 1.** Non- lethal effects of a single exposure. Exposure of cynomolgus monkey to HCN vapours led to incapacitation after 8 minutes in a concentration of 180 mg/m^3 and after 19 minutes in 110 mg/m^3. While 30 min exposure to HCN concentration of 110 mg/m^3 induced semi consciousness, respiratory disorders and EEG changes, concentration of 70 mg/m^3 led only to slight nervous depression. (**9**).
Conclusions:	1) For rats, LC_{50} values ranged from 158 mg/m^3 for a 60 minute exposure to 3778 mg/m^3 for 10 sec exposure. 2) The reliability of these estimates is supported by similar values found in other animal species and in other studies. 3) Human fatal concentrations from case reports fall into the same range. 4) LC_{50} values increased linearly with square root of the inverse value of exposure time between 30 minutes and 10 seconds: $Ln(LC_{50}) = 9.53 - 0.56 \ln t$, t time in seconds., R-squared = 99.17%. (Similar regression is reported in the study by McNerney et al. for cyanogen**: this study is summarised in section 6.1.3a.**) LC_{50} values increase much slower in the range of longer exposures, when the cumulation of cyanide is efficiently counterballanced by transformation to thiocyanate.

Table 1 Acute toxicity – inhalation (hydrogen cyanide)

Study		**Test organism**	**Exposure time**	**HCN concentration**	**Reference**
LC50 inhalatory	HCN	Rat Wistar Male	5 minutes	563mg/m^3 (503ppm)	(2)
LC50 inhalatory	HCN	Rat not specified	60 minutes	160mg/m^3 (143ppm)	**(1)**
LC50 inhalatory	HCN	Mouse ICR Male	5 minutes	362mg/m^3	(2)
LC50 inhalatory	HCN	Mouse ICR Male	3 minutes	448mg/m^3 (400ppm)	(3)
LC50	HCN	Mouse	30 minutes	180mg/m^3	**(4)**

inhalatory		Swiss-Webster Male		(166ppm)	
LC50 inhalatory	HCN	Rabbit Not specified	35 minutes	207mg/m^3 (188ppm)	**(1)**
LC50 inhalatory	HCN	Dog	3 minutes	336 mg/m^3 300ppm	(5)
LC50 inhalatory	HCN	Mouse	30 minutes	189 mg/m^3 169ppm	(5)
LC50 inhalatory	HCN	Rat	30 minutes	179 mg/m^3 160ppm	(6)

Table 2 Acute inhalation toxicity of hydrogen cyanide for rats in dependence on the exposure time (ref. 1)

Exposure time	LC_{50} (mg.m^{-3})
10 s	3778
1 min	1471
5 min	493
30 min	173
60 min	158

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Section A6.1 **Annex Point IIA VI.6.1**		**ACUTE TOXICITY**	
Section A6.1.3 **Annex Point IIA VI.6.1.3**		**Acute Inhalation Toxicity**	
		1 REFERENCE	**Official use only**
1.1	**Reference**	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)**	
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 (methods used comparable to guideline of Acute Inhalation Toxicity)	
2.2	**GLP**	No, study older than GLP	
2.3	**Deviations**	No	
		3 MATERIALS AND METHODS	
3.1	**Test material**	Cyanogen (NCCN)	
3.1.1	Lot/Batch number	Not reported	
3.1.2	Specification	Cyanogen gas	
3.1.2.1	**Description**	Colourless gas	
3.1.2.2	**Purity**	99.5% (0.5% - nitrogen, chlorine, cyanogen chloride)	
3.1.2.3	**Stability**	Not reported	
3.2	**Test Animals**		
3.2.1	Species	Rat	
3.2.2	Strain	Albino rat – strain not reported	
3.2.3	Source	Not reported	
3.2.4	Sex	Males only	
3.2.5	Age/weight at study initiation	Rat – 135 g (average)	
3.2.6	Number of animals per group	13 groups of six rats – six different concentrations, six different time periods and control	
3.2.7	Control animals	Yes	

3.3	**Administration/ Exposure**	Inhalation	
3.3.1	Post exposure period	14 days observation	
3.3.2	Concentrations	Nominal concentration : 0, 533, 537, 851, 851, 1054, 1066, 2115, 2111, 4207, 4223, 8508, 8571 mg/m³ (0, 250, 250, 400, 400, 500, 500, 1000, 1000, 2000, 2000, 4000 and 4000 ppm)	
		Analytical concentration – not reported	
3.3.3	Particle size	/	
3.3.4	Type or preparation of particles	/	
3.3.5	Type of exposure	Whole body	
3.3.6	Vehicle	No	
3.3.7	Concentration in vehicle	/	
3.3.8	Duration of exposure	120, 60, 45, 30, 15, 7.5 and 0 minutes.	
3.3.9	Controls	Not reported	
		4 RESULTS AND DISCUSSION	
4.1	**Clinical signs**	Acute Inhalation Toxicity: asphyxiation, lacrimation, upper respiratory tract irritation, pink coloration of the noticeable skin, blinking eyes, rubbing of forepaws over eyes and snout, huddling together with inactivity, slow gasping, tearful eyes, yellow fluid dripping from nares and mouth, restless and panic type movements, accentuated and poorly coordinated motions, bright pink coloration of the skin, laboured breathing, gasping, tremors, sluggishness, prostration, shallow breathing, death.	
4.2	**Pathology**	No effects reported	
4.3	**Other**	None	
4.4	**LC_{50}**	LC_{50} for cyanogen = 23,400 ppm / t; t= exposure duration in min See **Table II** - Effects of the Acute Inhalation Exposures of Cyanogen Upon Male Albino Rats and Inhalation toxicity of cyanogen in rats – time/concentration graph – **see Figure 1.**	
		5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	Non-guideline studies Rats were housed in wire mesh cages within the chamber and exposed to a total of six different concentrations of cyanogen and six different time periods. Survivors were observed for 14 days after exposure. Body weight of rats was measured before exposure and after 14 days.	
5.2	**Results and discussion**	The present study showed that rats withstood 250 ppm of cyanogen for 120 minutes with only partial mortality and 500 ppm for 30 minutes with no deaths. In addition, the capacity of the rats in this study to tolerate the excessive concentrations of 1000 and 2000 ppm of cyanogen for periods of approximately 15 and 7.5 minutes, respectively, points toward a lower toxicity.	

5.3 Conclusion	Assuming transformation of one molecule of cyanogen to one molecule of hydrogen cyanide, following approximate LC values may be calculated for HCN (:t= exposure duration in min): LC_0 = 15,900 mg/m^3 / t; LC_{50} = 25,850 mg/m^3 / t; LC_{100} = 41,050 mg/m^3 / t	
5.3.1 Reliability	2	
5.3.2 Deficiencies	The study from 1960 is not in the GLP system, but the method used is comparable to methods standardised by EU directive 440/2008.	

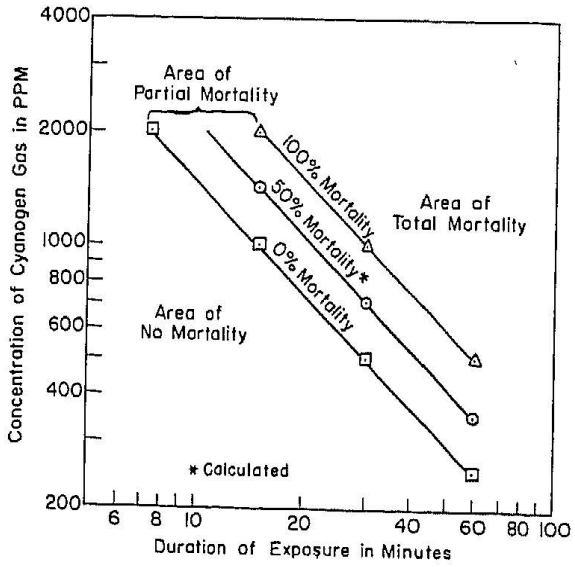

FIGURE 1. Inhalation toxicity of cyanogen in rats.

TABLE II

Effects of the Acute Inhalation Exposures of Cyanogen Upon Male Albino Rats

Concentration of Cyanogen (ppm)	Concentration of Cyanogen (mg/m³)	Average Temp. (°C)	Length of exposure (minutes)	Length of build-up period (minutes)	Mortality ratio (dead/dosed)	Initial average weight of rats (grams)	Average weight gain after 14 days (grams)
4000	8571	22.8	7.5	3.0	3/6	162	44
4000	8508	25.0	15	3.0	6/6	156	—
2000	4223	27.2	7.5	1.5	0/6	126	55
2000	4207	28.3	15	1.5	6/6	121	—
1000	2111	27.2	15	0.5	0/6	123	52
1000	2115	26.7	30	0.5	6/6	123	—
500	1066	24.4	30	0.3	0/6	134	49
500	1054	27.8	45	0.3	6/6	122	—
400	851	25.0	45	0.25	0/6	144	46
400	851	25.0	60	0.25	6/6	137	—
250	537	22.2	60	0.15	0/6	160	59
250	533	24.4	120	0.15	4/6	127	38
Control	—	—	—	—	0/6	167	53

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Section A6.1 Annex Point IIA VI.6.1	**ACUTE TOXICITY**	

Section A6.1.4 Annex Point IIA VI.6.1.4	**Skin Irritation**	
Justification: Supportive data:	No formal study on irritating effects of cyanides on skin in humans or animals is known and no such study can be realised with regard to easy penetration of HCN through skin and extremely high acute toxicity. Data from the observation of HCN effects on human skin, resulting from the observation performed during HCN and cyanides use, are reported as surrogate information. None of the observation data meet requirements for labelling of hydrogen cyanide as a skin irritating substance, resulting from the requirements for substance classification according (ES) 1272/2008. 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**).	
Reference:	1. Blanc P, Hoan M, Mallin K, et al. 1985. Cyanide intoxication among silver-reclaiming workers. J Am Med Assoc 253: 367-371 **(DOC IV_19)** 2. El Ghawabi SH, Gaafar MA, El-Saharti AA, et al. 1975. Chronic cyanide exposure: A clinical, radioisotope, and laboratory study. Br J Med 32:215-219 **(DOC IV_20)** 3. McNerney JM, Schrenk HH. 1960. The acute toxicity of cyanogen. Am Ind Hyg Assoc J 21:121-124 **(DOC IV_18)** 4. Fairley A, Linton EC, Wild FE. 1934. The absorption of hydrocyanic acid vapours through the skin with notes on other matters relating to acute cyanide poisoning. J Hyg 34: 283-294 **(DOC IV_21)**	
Guidelines:	Not presented	
GLP:	No	
Findings:	Cyanide caused rash in 42 workers exposed to 15ppm HCN. **(1)** Brick-red burns were observed in a man exposed to 200ppm HCN for an unspecified time. No skin inflammation was observed in workers exposed to 6.4–10.4 ppm of sodium cyanide and copper cyanide. **(2)** No dermal damage was observed on rabbit skin after exposure to 10,000ppm of cyanogen for 8 hours**. (3)** Vascular congestion was observed in skin of a guinea pig after exposure to unknown doses of hydrogen cyanide for 65 minutes. **(4)**	
Conclusion:	Hydrogen cyanide does not show signs of a skin irritating substance despite the fact that skin penetration is considered to be a possible route of exposure, **see Doc 6.1.2.** Notes: - Dermal rash in silver reclaiming workers (**1**) are described on the basis of anamnestic data (questionnaire); concentrations of HCN in the hall should have been enormous: the investigation has been prompted by a case of acute fatal HCN poisoning; in	-

	addition, workers of silver reclaiming factory had been exposed to many chemical substances that may cause rash. - The skin of guinea pig was exposed to saturated vapours of HCN (i.e. approx. 915g/m^3) Cyanogen as surrogate for dermal irritation by HCN can be justified as it is likely to be hydrolysed to cyanide and cyanate during skin penetration.	

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Section A6.1 Annex Point IIA VI 6.1	**ACUTE TOXICITY**	

Section A6.1.4 Annex Point IIA VI.6.1.4	**Eye Irritation**	
Justification: Supportive data:	No formal study on irritating effects of cyanides on eyes in humans or animals is known and no such study can be realised with regard to extremely high acute toxicity. Data from the observation of HCN effects on human eyes, resulting from the observation performed during HCN and cyanides use, are reported as surrogate information. None of the observation data meet requirements for classification of hydrogen cyanide as irritating to eyes. 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**).	
Reference:	1. McNerney JM, Schrenk HH. 1960. The acute toxicity of cyanogen. Am Ind Hyg Assoc J 21:121-124 **(DOC IV_18)** 2. Bonsall JL. 1984. Survival without sequelae following exposure to 500 mg/m^3 hydrogen cyanide. Hum Toxicol 3:57-60 **(DOC IV_22)** 3. Chandra H, Gupta BN, Ghargava SK, et al. 1980. Chronic cyanide exposure: A biochemical and industrial hygiene study. J Anal Toxicol 4:161-165. 4. Blanc P, Hogan M, Mallin K, et al. 1985. Cyanide intoxication among silver-reclaiming workers. J Am Med Assoc 253: 367-371 **(DOC IV_19)** 5. El Ghawabi SH, Gaafar MA, El-Saharti AA, et al. 1975. Chronic cyanide exposure: A clinical, radioisotope, and laboratory study. Br J Med 32:215-219 **(DOC IV_20)** 6. BRYAN BALLANTYNE, M.D., D.Sc., Ph.D., 1983, Acute systemic 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), **summary see Section 6.1.2c) (DOC IV_16)** 7. Bryan Balantyne, 1988, Toxicology and Hazard Evaluation of Cyanide Fumigation Powders, Applied Toxicology Department, Union Carbide Corporation, Danbury, Connecticut 06817, Clinical Toxicology, 26 (5&6), 325-335; **summary see Section 6.1.2a and Section 6.1.2b. (DOC IV_14)**	
Guidelines:	None.	
GLP:	No	
Material and methods:	Observation in volunteers and in workers. Observation in animals tested for inhalation toxicity or for systemic toxicity of HCN applied into the conjunctival sac.	
Findings:	Cyanogen caused eye irritation in volunteers during short exposure to 16ppm **(1).** A negligible loss of peripheral vision was the only permanent effect observed in a man, whose eyes had been exposed to 452 ppm HCN for	

	13min during tank cleaning. **(2)** Eye irritation in two workers engaged in electrolytic coating was observed during chronic occupational exposure. **(3)** In other studies, cyanides caused eye irritation in 5 workers exposed to 15ppm HCN **(4)**, and lacrimation in workers exposed to 6.4 ppm of cyanide. **(5)**. Eye irritation may not be caused solely by cyanides; workers engaged in electrolytic coating may be exposed also to other chemicals irritating to eyes. Data on eye effects for animals by inhalation are available only for rats which were acutely exposed for 7.5-120 minutes to 250 ppm cyan, and 125ppm cyanide. **(1)** Tight belepharospasm after application of 3 – 4% HCN water solution indicates acute irritation. **(6)** Local signs of irritancy and inflammation were seen promptly after placing NaCN in the inferior conjunctival sac, and considered of marked lachrymation, moderate conjuctival hyperemia and mild chemosis. Conjuctivitis and lachrymation slowly resolved after 24 hours, but mild residual inflammation was still present at 7 days **(7).**	

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Section A6.1 **Annex Point IIA VI.6.1**		**ACUTE TOXICITY**	
Section A6.1.4 **Annex Point IIA VI.6.1.4**		**Acute Eye Irritation**	
		1 REFERENCE	**Official use only**
1.1	**Reference**	Bryan Ballantyne, 1988, Toxicology and Hazard Evaluation of Cyanide Fumigation Powders, Applied Toxicology Department, Union Carbide Corporation, Danbury, Connecticut 06817, Clinical Toxicology, 26 (5&6), 325-335 **(DOC IV_14)**	
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 (method used comparable to guideline of Acute Toxicity: Eye Irritation/Corrosion)	
2.2	**GLP**	Not reported	
2.3	**Deviations**	No	
		3 MATERIALS AND METHODS	
3.1	**Test material**	NaCN powder	
3.1.1	Lot/Batch number	Not reported	
3.1.2	Specification	Pure NaCN	
3.1.2.1	**Description**	Powder	
3.1.2.2	**Purity**	Pure	
3.1.2.3	**Stability**	Not reported	
3.2	**Test Animals**		
3.2.1	Species	Rabbit	
3.2.2	Strain	New Zealand white	
3.2.3	Source	Not reported	
3.2.4	Sex	Females only	
3.2.5	Age/weight at study initiation	Rabbits: 1770.0 – 2470.0 g (age – not reported)	
3.2.6	Number of animals per group	10 animals/each dose	
3.2.7	Control animals	Not reported	
3.3	**Administration/ Exposure**	Ocular – into the inferior conjunctival sac of one eye	

3.3.1	Preparation of test substance	Test substance was used as delivered.	
3.3.2	Amount of active substance instilled	3.18 – 9.96 mg/kg	
3.3.3	Exposure period	Not reported	
3.3.4	Post exposure period	7 days	
3.4	**Examinations**	Examination of eyes and examination of systemic signs of toxicity	
3.4.1	Ophthalmoscopy examination	Not reported	
3.4.1.1	**Scoring system**	Not reported	
3.4.1.2	**Examination time points**	1. immediately after application 2. 24 hours after exposure 3. 7 days after exposure	
3.4.2	Other investigations	/	
		4 RESULTS AND DISCUSSION	
4.1	**Clinical signs**	1. immediately after application: marked lacrimation, moderate conjunctival hyperaemia, mild chemosis; 2. in survivors – 24 hours after exposure: more severe conjunctival hyperaemia, mild to moderate corneal opacification and mild iritis after 24 hours; 3. in survivors – 7 days after application: mild conjunctival inflammation and mild to moderate keratitis Systemic clinical signs: rapid breathing, weak movements, tremors, respiratory distress, severe spasms, convulsions, irregular shallow breathing, coma, death.	
4.2	**Average score**		
4.2.1	Cornea	Score – not reported	
4.2.2	Iris	Score – not reported	
4.2.3	Conjunctiva	Non-entry field	
4.2.3.1	**Redness**	Score – not reported	
4.2.3.2	**Chemosis**	Score – not reported	
4.3	**Reversibility**	Rabbits were observed only for 7 days - mild conjunctival inflammation and mild to moderate keratitis were observed.	
4.4	**Other**		
4.5	**Overall result**		
		5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	The test substance (NaCN powder) was applied into the inferior conjunctival sac of one eye of rabbits – several groups of animals with various dose levels. Following exposure animals were observed for signs of toxic effects and for local signs of eye irritation. Survivors were kept only for 7 days.	

5.2	**Results and discussion**	Application of NaCN powder to rabbit eye caused a rapid onset of moderately severe conjunctivitis and keratitis. Mild conjunctival inflammation and mild to moderate keratitis were observed in survival animals 7 days after application. Lethal systemic toxicity was also produced by contamination of rabbit eye with NaCN powder.	
5.3	**Conclusion**	Application of NaCN powder conjunctival sac caused a rapid onset of moderately severe conjunctivitis and keratitis, persisting at least 7 days.	
5.3.1	Reliability	*2*	
5.3.2	Deficiencies	Scoring system is not specified, post-exposure observation is too short.	

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Section A6.1 Annex Point IIA VI.6.1	**ACUTE TOXICITY**	

Section A6.1.5 Annex Point IIA VI.6.1.5	**Skin Sensitisation**	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ]	**Technically not feasible [x] Scientifically unjustified [x]**	
Limited exposure [ ]	**Other justification [ ]**	
Justification:	It is practically difficult, if not impossible, to conduct a specific study on skin contact sensitization with hydrogen cyanide vapours; when applied on skin in a water solution hydrogen cyanide is also easily resorbed and causes acute systemic poisoning. To our knowledge, there are no confirmed cases in humans to suggest that hydrogen cyanide is a skin sensitizer. Hydrogen cyanide does not present any structural alert for skin sensibilization, standard skin sensibilization test is not feasible and sensibilization properties of cyanides have not been suggested by the experience in humans over a period of many years of production and use. This conclusion is supported by exhaustive and reliable 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		
Conclusion	There are no confirmed cases in humans to suggest that hydrogen cyanide is a skin sensitizer.	
Undertaking of intended data submission	No studies are planned.	

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Section A6.12 **Annex Point IIA VI.6.9**	**MEDICAL DATA IN ANONYMOUS FORM**
Justification:	Hydrogen cyanide has been used for many years and its effects on humans in occupational settings are well known. Data for cyanides (in diet) are used as supporting information for oral exposure.
References:	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 (state in February 2006): Hydrogen cyanide *Peer reviewed* **(DOC IV_2).** **Summaries of two case studies are in DOC III 6.12.1a and b** (ref. 69 and 72). References from ATSDR, 2004, IPCS and HSDB: 1. American Conference of Governmental Industrial Hygienists (ACGIH); Documentation of the Threshold Limit Values and Biological Exposure Indices. 5th ed. Cincinnati, OH: American Conference of Governmental Industrial Hygienists, 1986., p. 314 2. Banerjee KK, Bishayee B, Marimuthu P (1997) Evaluation of cyanide exposure and its effect on thyroid function of workers in a cable industry. Journal of Occupational Medicine, 39:255–260. 3. Drinker P. 1932. Hydrocyanic acid gas poisoning by absorption through the skin. J Ind Hyg 14:1-2. 4. Dudley HC, Sweeney TR, Miller JW. 1942. Toxicology of acrylonitrile (vinyl cyanide). II: Studies of effects of daily inhalation. J Ind Hyg Toxicol 24:255-258 5. Chandra H, Gupta BN, Mathur N. 1988. Threshold limit value of cyanide: A reappraisal in Indian context. Indian J Environ Protection 8:170-174. 6. VanderLaan WP, Bissell A. 1946. Effects of propylthiouracil and of potassium thiocyanate on the uptake of iodine by the thyroid gland of the rat. Endocrinology 39:157-160. 7. ATSDR (1993) Toxicological profile for cyanide. Prepared by Syracuse Research Corporation under subcontract to Clement International Corporation (Contract No. 205-88-0608). 8. ATSDR (1991) Case studies in environmental medicine. Atlanta, GA, US Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry 9. Hardy HL, Jeffries WM, Wasserman MM, Waddell WR (1950) Thiocyanate effect following industrial cyanide exposure. New England Journal of Medicine, 242:968–972. 10. Leeser JE, Tomenson JA, Bryson DD (1990) A cross-sectional study of the health of cyanide salt production workers. Macclesfield, ICI Central Toxicology Laboratory. 11. Okafor PN, Okorowko CO, Maduagwu EN (2002) Occupational and dietary exposures of humans to cyanide poisoning from large-scale cassava processing and ingestion of cassava foods. Food and Chemical Toxicology, 49:1001–1005. 12. Linden CH, Lovejoy Jr. FH. 1998. Poisoning and drug overdose. In: Fauci AS, Braunwald E, Isselbacher KJ, eds. Harrison's principles of internal medicine. New York: McGraw-Hill Health; Professions Division. 13. Berlin C. 1977. Cyanide poisoning--A challenge. Arch Intern Med 137:993-994. 14. Williams, 1959 – Williams RT (1959) Detoxification mechanisms, 2nd

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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