KAROLINSKA INSTITUTET
Institute of Environmental Medicine
Work Environment Toxicology
Gunnar Johanson

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Ångpanneföreningens forskningsstiftelse
Box 8133
104 20 Stockholm

Slutrapport för projektstöd avseende projektet
”Diagnos av cyanidförgiftning vid bränder via analys av utandningsluft”
(ref nr 06-071)

Många människor dör årligen av brandrök i samband med bränder. Kolmonoxid torde vara den viktigaste enskilda orsaken, men cyanväte (HCN) är troligen en starkt underskattad orsak. HCN avges från många moderna material då de brinner, bl.a. möbelstoppning av ployuretanskum. Cyanidförgiftning kan även uppkomma till följd av terroristattacker och vid industriell cyanidhantering. Cyanidförgiftning är livshotande och behandling, fr.a. med antidot, måste snabbt initieras. I dag saknas en snabb metod att diagnosticera cyanidförgiftning.

Det långsiktiga målet med projektet, som delvis finansierats via ÅF, är att om möjligt ta fram en metod att snabbt diagnosticera cyanidförgiftning via analys av utandningsluft (UL). Projektets delmål är att besvara följande frågor:

1. Vilka HCN-nivåer uppstår i UL pga washout från andningsvägarna efter hög, kortvarig med ofarlig exponering?
2. Vad är bakgrundsnivån av HCN i UL hos icke cyanid-exponerade personer?
3. Ökar HCN i UL efter akut systemisk cyanidförgiftning?
4. Utveckling av en snabb, enkel och tillförlitlig direktvisande detektor för HCN i UL.
5. Samband mellan HCN i UL och i blod

De tre första delstudierna har helt eller delvis genomförts, vilka kortfattat beskrivs nedan. Arbetena kommer att ingå i Kristin Stamyrs doktorsavhandling.

Delstudie 1
I den första delstudien undersökte vi den s.k. washin–washout effekten. HCN är mycket vattenlösligt, vilket gör att ämnet under inandningen absorberas i vätskeskiktet som bekläder epitelet i andningsvägarna. Under utandningen avgår i stället ämnet till luften. Denna washin–washout effekt kan störa eller omintetgöra möjligheten att använda HCN i UL som indikator för cyanidförgiftning, eftersom en stor del av uppmätt HCN då kan härröra från nyligen inträffad, kortvarig men hög (och ofarlig), inhalationsexponering och inte från längre livshotande exponering. Vi mätte tidsförloppet av HCN i UL med en elektrokemisk detektor hos tio friska, frivilliga försökspersoner under och efter 60 sekunders exponering för 10 ppm HCN (motsvarar ungefär den mängd man inhalerar om man röker en cigarett). Avklingningen av HCN hade en halveringstid på 16 sek (intervall 10-24) sek. Extrapolering till höga exponeringsnivåer indikerar att bidraget från

Postal address	*Visiting address*	*Telephone*	*Fax*	*E-Mail*
Box 210	Nobels väg 13	+46 8 5248 6400	+46 8 31 41 24	Gunnar.Johanson@ki.se
SE-171 77 STOCKHOLM	SOLNA	+46 8 5248 7752 (direct)		

washin-washout är försumbart även vid livshotande exponeringsnivåer. Arbetet, *Washout kinetics of inhaled hydrogen cyanide in breath,* har publicerats i Toxicology Letters (artikeln bifogas).

Delstudie 2
För att kunna identifiera förhöjda HCN-nivåer i UL behövs data på ”normala” bakgrundsnivåer av HCN i UL. I delstudie 2 har vi därför undersökt detta på 40 friska frivilliga försökspersoner (26 män och 14 kvinnor i åldern 21-61 år. Mätningarna utfördes i samarbete med Helsingfors universitet med hjälp av en nyutvecklad metod, cavity ring down spectroscopy (CRDS). Instrumentet använder en pulsad laser I det infraröda området och har extremt hög känslighet. Vi detekterade HCN hos 39 av de 40 personerna (median 4,4, intervall <1.5 - 14 ppb). Studien antyder att kvinnor har en något högre HCN-nivå än män, däremot sågs inget samband med rökvanor, måltider eller ålder. Arbetet har resulterat i ett manus med titeln *Background levels of HCN in human breath measured by cavity ring down spectroscopy*, som inom kort kommer att skickas till en vetenskaplig tidskrift (tillsänds ÅF när arbetet kommit i tryck).

Delstudie 3
Målsättningen med delstudie 3 är att med hjälp av en fysiologiskt baserad toxikokinetisk (PBTK) model beräkna förväntade nivåer av HCN i UL efter en livshotande cyanidexponering. En ny PBTK-model har utvecklats med ändamålet att beskriva toxikokinetiken för cyanid hos människa. I denna typ av modeller representeras kroppens vävnader och organ av s.k. compartments. De toxikokinetiska processerna absorption, distribution, metabolism och elimination (ADME) beskrivs genom att via massbalansekvationer simulera tidsförloppen i blod, olika organ och UL över tid under och efter olika exponeringar för HCN. Modellen utnyttjar kända anatomiska (t.ex. organvolymer) och fysiologiska (t.ex. blodflöden) data, samt alla tillgängliga relevanta data över HCN. Resultaten från simuleringarna tyder på att förväntade HCN-nivåer i UL ligger omkring några hundra ppb, vilket är avsevärt högre än bakgrundsnivåerna enligt delstudie 2. Ett utkast till manus, med arbetsnamnet *Physiologically-based toxicokinetic and toxicodynamic modelling of cyanide in human breath* föreligger (tillsänds ÅF när arbetet kommit i tryck).

Vänliga hälsningar

Gunnar Johanson, professor och enhetschef
Projektansvarig

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Washout kinetics of inhaled hydrogen cyanide in breath

Kristin Stamyr*, Pierre Nord, Gunnar Johanson

Work Environment Toxicology, Institute of Environmental Medicine, Karolinska Institutet, SE-171 77 Stockholm, Sweden

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ABSTRACT

Hydrogen cyanide (HCN) intoxication causes or contributes significantly to many of the fatalities among fire victims. To enable fast treatment of HCN poisoning, a more rapid diagnostic method than currently available is required. One possibility would be measurement in exhaled air. However, as HCN is highly water soluble, it may be absorbed during inhalation and reabsorbed during exhalation. If this, so-called, washin–washout effect is substantial it may interfere with the diagnosis, as a major part of breath HCN may originate from the respiratory tract, due to recent exposure, and not from systemic exposure. The aim of this study was to estimate the importance of the washin–washout effect of HCN. The time-course of cyanide in exhaled air was measured with an electrochemical detector in 10 volunteers during and after a 1 min × 10 ppm exposure to HCN. The experiment revealed an average half-life of 16 s (range 10–24 s) in breath. Extrapolating the results to higher exposures suggests that the contribution from washin–washout from the airways will be negligible even at fatal exposures. The results support the use of breath HCN as a potential indicator of systemic intoxication.

1. Introduction

For people caught in fires, or fire fighters entering fires, a major threat is posed by the release of toxic fumes. Between 60 and 80% of all deaths related to fire are attributed to such fumes (Barillo et al., 1986). Carbon monoxide (CO) is a major component and is commonly thought to be the major cause of most fire-related intoxications and fatalities (Simonson et al., 2001). Hydrogen cyanide (HCN) is another toxic gas that is formed, especially during combustion of materials containing nitrogen, such as wool and polyurethane foam (Purser, 2000; Simonson et al., 2001). These materials are frequently and increasingly encountered in homes and indoor dwellings (Alarie, 2002).

The exact contribution of HCN in fire related deaths, e.g. in relation to CO, is difficult to assess, due to breakdown of cyanide in blood post mortem (Moriya and Hashimoto, 2001, 2003) and the lack of rapid analytical methods (Baud, 2007; Hall et al., 2007). However, a couple of studies suggest that HCN is an important or even major contributing factor to a fatal outcome (Purser, 2000; Simonson et al., 2001). One reason is that cyanide has a strong "knock down" effect, i.e. a fire victim could lose consciousness due to high concentrations of HCN, consequently preventing an escape, and thereafter die due to CO poisoning, or both combined (Purser, 2000).

An idea of the magnitude of the problem may be obtained by some data from USA and Sweden. Between 3245 and 3925 persons (11–14 per million inhabitants) died annually in fires during 2002–2006 in the US (Karter, 2007; USFA, 2007). Similarly, between 65 and 138 people (7–15 per million) died each year in fires in Sweden during the period 2002–2006 (Erlandsson, 2007).

The distinction between CO and HCN as a cause of life-threatening intoxication in fire victims is crucial for rapid treatment. Today, fire victims are routinely treated with oxygen already at the fire scene (Baud, 2007; Hall et al., 2007) thus, reducing the body burden of CO. Cyanide intoxication on the other hand, should be treated with antidotes. A number of antidotes are used or have been proposed for treatment of cyanide poisoning, including methaemoglobin-forming substances (e.g. amyl nitrite), cobalt compounds (e.g. hydroxocobalamin), sulphur donors (e.g. sodium thiosulfate) and cyanohydrin-forming agents (e.g. alpha-ketoglutarate) (Bhattacharya and Vijayaraghavan, 2002; Baud, 2007; Hall et al., 2007). Hydroxocobalamin and sodium thiosulfate have been suggested as the preferred antidotes (Hall et al., 2007). Regardless of choice of antidote, such treatment requires intravenous catheterization and is only carried out if the victim is diagnosed as being intoxicated by cyanide. However, the diagnosis is difficult to establish at the fire scene. Apart from the difficulties with blood sampling at the fire scene, there is currently no method available for field measurement of blood cyanide (Baud, 2007). A non-invasive, rapid test

* Corresponding author at: Work Environment Toxicology, Institute of Environmental Medicine, Karolinska Institutet, Nobels väg 13, P.O. Box 210, SE-171 77 Stockholm, Sweden. Tel.: +46 8 524 87709; fax: +46 8 314 124.
E-mail address: kristin.stamyr@ki.se (K. Stamyr).

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method for cyanide intoxication would enable faster and safer diagnosis.

One way of detecting cyanide intoxication is by smelling the exhaled breath from the patient. HCN smells of bitter almonds with an odour threshold of about 0.2–5 ppm (Musshoff et al., 2002). Major drawbacks of such an olfactory method is that the odour threshold may be too high and that many individuals are unable to smell HCN at all (Holland and Kozlowski, 1986). An additional problem is that the smell of HCN is masked by many other components present in fire smoke (Baud, 2007). Still, it indicates that breath HCN might be a valuable tool in the diagnosis of cyanide intoxication, provided that a practical and robust analytical method is available, as exhaled air is much more easily sampled than venous blood at the fire scene.

The underlying assumption is that HCN in breath reflects the body burden. For this assumption to be valid, the HCN detected in exhaled air should originate from the systemic circulation and not from the respiratory tract. In other words, the exhalation of HCN that was absorbed in the epithelial linings of the respiratory tract during the preceding inhalation should be negligible. This is not obvious, as HCN is polar and water soluble with a water:air partition coefficient of 160 (calculated from Edwards et al., 1978). Respiratory washin–washout phenomena have been described for other polar substances, such as acetone (Johanson, 1991; Mörk and Johanson, 2006). If the washin–washout effect is significant for HCN, high levels in exhaled air will mainly reflect recent, brief exposures to high air levels of HCN. If, on the other hand, the washin–washout effect is negligible, HCN in breath will mainly reflect the systemic dose. In this case, a high HCN concentration in breath may indicate cyanide intoxication.

The aim of the present study was to elucidate the importance of the washin–washout effect for inhaled HCN. This was done by exposing healthy volunteers to low levels (10 ppm or 11 mg/m^3) of HCN for 1 min, and tracing the profile in exhaled air. The inhaled dose (110 μg HCN, assuming a lung ventilation of 10 L/min) is comparable to that obtained from smoking one cigarette (4–199 μg HCN, Roemer et al., 2004).

2. Material and methods

2.1. Subjects

Six females and four males, between 22 and 58 years old, participated in the study. HCN exposure was carried out following a health questionnaire and a general physical examination. The subjects were included in the study only if considered healthy. The following inclusion criteria were used: non-smoker, no history of chronic disease, no use of pharmaceuticals, and furthermore, a pregnancy test (SureStep, San Diego, USA) was conducted immediately before exposure confirming that no subjects were pregnant. The volunteers were informed verbally and in writing about the design of the study, possible hazards, and their right to abort participation whenever they wanted. The study was approved by the Regional Ethical Review Board in Stockholm, and performed following informed consent and according to the Helsinki declaration.

2.2. Chemicals

Potassium cyanide (BioChemika Ultra, ≥98.0%) was purchased from Fluka Chemie (Buchs, Switzerland). Sodium hydroxide (p.a. > 99%) and phosphoric acid (99%) was obtained from Merck (Darmstadt, Germany). HCN (99.99% purity), 10 ppm (11 mg/m^3) in synthetic air, was supplied by AGA (Unterschleißheim, Germany).

2.3. Experimental design

One subject at a time was exposed to 10 ppm HCN for 1 min via a rubber mouthpiece connected with two unidirectional valves for inhalation and exhalation to a polyester-laminated aluminium bag containing the HCN vapour (Fig. 1). The laminated bag was filled with 20 L air containing 10 ppm HCN, either by direct filling from the gas cylinder supplied by AGA or by generation from potassium cyanide (KCN). To generate HCN, 2 mL of 42 mM KCN and 2 mL 0.1 M NaOH was transferred to a wash bottle containing 10 mL distilled water. The wash bottle was placed in a temperature controlled water bath (70 °C), 2 mL of phosphoric acid was added and the wash bottle was immediately capped. The released HCN was transferred to the laminated bag by pumping 20 L of clean air though the wash bottle. The pump (Aircheck Model 224-PCXR8, SKC) was calibrated to 3.00 L/min and was run for 6.67 min. With a recovery of 100%, this corresponds to a concentration of 10 ppm HCN in the bag. The bags were filled approximately 30 min prior to the experimental exposure. Acid-generated HCN was used as a replacement for the HCN gas mixture supplied by AGA, as we were unable to order more of the latter. Considering the variable sensitivity of the electrochemical (EC) detector, both HCN sources generated similar detector responses, indicating that the recovery of acid-generated HCN was close to 100%.

The experiment started with a 5-min period with the subject breathing clean air in order to obtain an EC detector baseline and to make the subject feel comfortable with the equipment and the situation. The subject was instructed to breathe normally at all times. The exposure was then initiated by switching a valve (Fig. 1) from clean air to 10 ppm HCN. After the 1-min exposure the valve was switched back to clean air and the measurements continued for another 10 min. Inhaled/exhaled air was continuously sampled from the mouth orifice via a stainless-steel tubing to the EC detector (Interscan Compact Portable Analyzer, Model 4280-2, Interscan Corporation, Chatsworth, CA, USA). The analogue signal from the EC detector was logged on a personal computer via an analogue/digital converter with a sampling frequency of 1 s^{-1}. The time course of the HCN concentration was also visualized directly on-screen. The detector was calibrated to 10 ppm after the end of each exposure by pumping the HCN gas mixture from the bag. Thus, any variability in HCN concentration between sources or in detector sensitivity between experiments, were controlled for by normalisation. Pulmonary ventilation was continuously monitored by a respiratory meter (K.L. Engineering Haeger Gasanalysator AB, Model S-340, CA, USA) attached before the inhalatory valve. All material in contact with exhaled air was heated to 40 °C to avoid condensation. A nose clip was used to prevent nose-breathing.

Prior to exposure venous blood was sampled for determination of haemoglobin (Hb) and methaemoglobin (MetHb). The blood analyses were carried out at the Karolinska University Hospital (Stockholm, Sweden).

2.4. Kinetic calculations

The time course measured with the EC-detector was analysed with a first-order one-compartment model. The change in concentration in exhaled air (C_{exh}) during exposure to HCN is described by the differential equation:

$$\frac{dC_{exh}}{dt} = K_e(C_{ss} - C_{exh}) \quad (1)$$

where K_e is the elimination rate constant and the initial condition at $t = 0$ is $C_{exh} = 0$. The concentration at steady-state concentration (C_{ss}) is a constant fraction (F_{ss}) of the inhaled concentration (C_{in}), thus:

$$C_{ss} = F_{ss}C_{in} \quad (2)$$

C_{in} is 10 ppm during the 1-min exposure, thereafter it drops to 0 ppm. The observed concentration at the sampling site (C_{obs}) reflects a mix of inhaled and exhaled breath and is described by

$$\frac{dC_{obs}}{dt} = K_{det}(F_{inh}C_{in} + (1 - F_{inh})C_{exh} - C_{obs}) \quad (3)$$

where F_{inh} and $(1 - F_{inh})$ are the fractional contributions of inhaled and exhaled air, respectively. K_{det}, the rate constant for the detector response, was determined separately to 0.26 s^{-1} (range 0.23–0.29 s^{-1}), corresponding to 50% response in 2.7 s (range 2.4–3.0 s).

The delay in EC detector response (including the sampling tube) was tested beforehand and turned out to be approximately exponential. Thus, the observed concentration (C_{obs}) is described by

$$\frac{dC_{obs}}{dt} = K_{det}(C_{mix} - C_{obs}) \quad (4)$$

The kinetic parameters (F_{inh}, C_{ss} and K_e) were obtained by fitting the HCN time course of each subject using the Berkeley Madonna software (Version 8.0.1, Macey and Oster, Berkeley, CA). Relations between kinetic parameters and physiologic (haemoglobin and methaemoglobin levels, pulmonary ventilation) and demographic (age, gender) data were tested by linear regression analysis, using the R software (Version 2.3.1, the R Project for Statistical Computing), $p \leq 0.05$ was regarded as significant.

3. Results

The average time course of the concentration in mixed inhaled and exhaled air is shown in Fig. 2. The concentration increased rapidly in the beginning of the exposure and then started to level off at about 4.5 ppm, without reaching a steady state during the 1-min exposure at 10 ppm HCN. The post-exposure decrease was similarly rapid and was indistinguishable from the baseline after

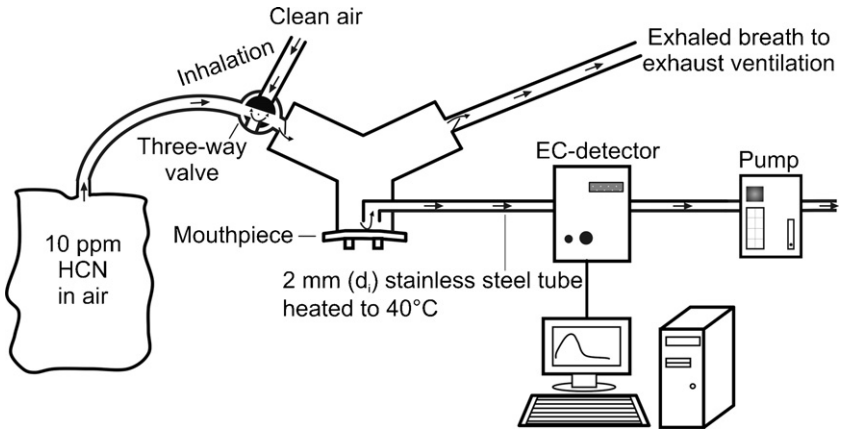

Fig. 1. A schematic description of the experiment setup where the volunteer is exposed to 10 ppm HCN gas for 1 min. Thereafter, the inhalation is switched to clean air. Breath is continuously pumped from the mouth orifice via a heated stainless tube to the electrochemical detector. Thus, the sample consists of a mixture of exhaled an inhaled breath. The results are logged to a personal computer.

1 min. The decline was biphasic, as seen in the log-normal graph (Fig. 2B).

Representative data from one of the 10 experiments (subject 8) along with the modelled curves, is shown in Fig. 3. The variations due to breathing is reflected as slight, cyclic variations in EC detector readout (marked as observed level in Fig. 3), however, the slow detector response cannot fully capture this cyclic behaviour. The estimated average steady-state level in mixed inhaled and exhaled air (fitted level in Fig. 3) was 4.5 ppm (S.D. 0.62). The lower curve in Fig. 3 shows the estimated concentration in exhaled breath. This curve takes the inhalation of 10 ppm HCN during part of the breathing cycle, as well as the delay in detector response, into account. In this subject (no. 8 in Table 1), the calculated steady-state concentration in exhaled air was 3.4 ppm, corresponding to a relative uptake of 66%. The average relative uptake at steady state of all 10 subjects was 70% (S.D. 6.6%) and the average half-life in exhaled breath was 15.6 s. For further data, see Table 1.

None of the kinetic parameters correlated significantly with pulmonary ventilation, age or gender, or with haemoglobin or methaemoglobin levels in blood. However, a tendency was seen ($p = 0.057$) for the pulmonary ventilation versus the relative uptake.

4. Discussion

To our knowledge, this is the first study that has investigated the kinetics of hydrogen cyanide in breath. Our findings suggest that the disappearance of HCN from the respiratory system, following a brief exposure of 1 min, is rapid with a half-life of between 10 and 22 s in exhaled breath. Ten subjects participated in this study. We deemed this to be sufficient, since the washout phenomena under study are expected to be affected mainly by physical rather than biochemical or enzymatic factors.

The model used to describe the HCN kinetics only includes the airways, while the rest of the body is considered as an infinite sink. Thus, elimination occurs by bulk flow via exhalation and by diffusion from the outermost layers lining the respiratory tract to the rest of the body. Both processes are likely to be of first order. Back diffusion from the body to the airways is thus considered to be negligible during the short time period of interest. This may be an oversimplification, as the semi logarithmic plot of the time course of HCN in breath (Fig. 2B) suggests a biphasic behaviour, with an

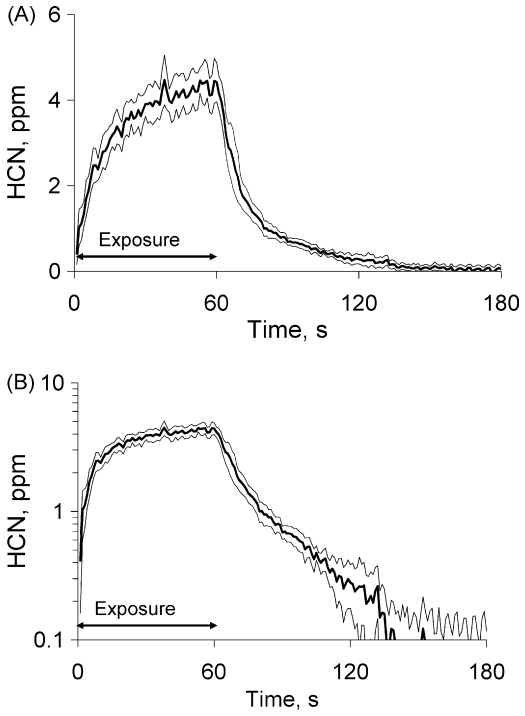

Fig. 2. Average concentration (thick line) of HCN in breath from 10 volunteers during and after inhalation exposure to 10 ppm HCN-gas for 1 min. The upper and lower 95% confidence intervals are indicated by thin lines. Concentrations are given on linear (A) and logarithmic (B) scales.

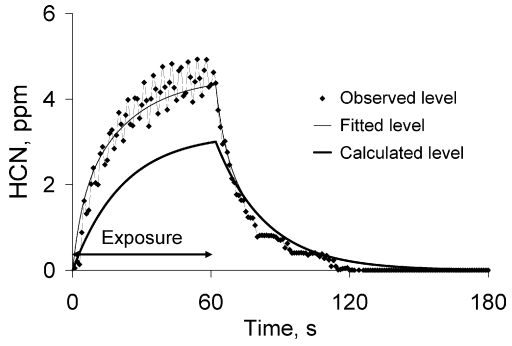

Fig. 3. Measured and modelled time course of HCN in breath from one subject exposed at 10 ppm HCN for 1 min. The fluctuating dotted curve represents measured values in mixed inhaled and exhaled breath. The thin curve shows the best fit to a one-compartment model. The lower (thick) curve shows the estimated concentration of HCN in exhaled breath.

Table 1
Ventilation rate and toxicokinetic parameters in 10 subjects exposed to 10 ppm HCN for 1 min

Subject number	Ventilation rate (L/min)	Inhalation (% of total breathing cycle)	Steady-state concentration in exhaled air (ppm)	Half-life in exhaled air (s)
1	–[a]	21.7	1.88	16.6
2	12.8	18.8	1.88	19.3
3	7.3	20.5	3.17	13.8
4	10.5	30.0	3.36	24.4
5	12.0	28.6	3.39	15.0
6	11.7	16.3	3.30	13.7
7	13.6	24.1	2.79	14.6
8	9.5	14.9	3.41	10.0
9	9.2	19.5	3.19	15.2
10	4.6	17.5	3.88	13.2
Mean	10.1	21.2	3.03	15.6
S.D.	2.9	5.0	0.66	3.9

[a] Not measured due to equipment failure.

apparently slower decrease rate (and, hence, a somewhat longer half-life) appearing at approximately 20 s post-exposure. This shift may represent a true biphasic pattern, as a back diffusion from deeper parts in the walls of the airways, suggesting a need for a two-compartment rather than a one-compartment model. Alternatively, the biphasic pattern is an artefact due to baseline drift resulting in erratic baseline correction. As we cannot rule out baseline drift, we have chosen to use the one-compartment model.

None of the kinetic parameters showed any correlation with the absolute or relative amount of haemoglobin, nor methaemoglobin. Since cyanide binds strongly to haemoglobin (Vesey et al., 1976) and even more so to methaemoglobin (Schulz, 1984), such correlations would have been expected, if there had been significant back diffusion from the systemic parts to the airways. Thus, one would have expected that more cyanide would bind to blood in subjects with more methaemoglobin, resulting in less back diffusion.

We propose that the use of HCN in breath as a diagnostic tool for cyanide poisoning should be further investigated. One possible concern with such a diagnostic tool would be that a brief, relatively harmless exposures to high concentrations of HCN could give rise to high breath levels for considerable time after the exposure, due to slow washout of HCN dissolved in the airways. A high breath HCN level might then indicate not only systemic washout of a toxic dose but also respiratory washout of a locally high, non-toxic dose, reducing its value as a diagnostic tool. However, extrapolating the results of the present study (with half-lives ranging from 10.0 to 24.4 s) to a 1-min exposure at 100 ppm HCN, shows that the breath level would range from 0.0001 to 20 ppb 5 min later. This range is below or close to the reported background breath levels of between 0 and 62 ppb (Lundquist et al., 1988; Španěl et al., 2007a,b).

In conclusion, our results suggest that the respiratory washout effect of HCN can be neglected. Thus, the concentration of hydrogen cyanide in breath might be used as an indicator of systemic cyanide intoxication. Further studies are required to describe the relation between breath HCN and degree of intoxication and to further characterize the background breath levels in the population.

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References

Alarie, Y., 2002. Toxicity of fire smoke. Crit. Rev. Toxicol. 32, 259–289.
Barillo, D.J., Rush Jr., B.F., Goode, R., Lin, R.L., Freda, A., Anderson Jr., E.J., 1986. Is ethanol the unknown toxin in smoke inhalation injury? Am. Surg. 52, 641–645.
Baud, F.J., 2007. Cyanide: critical issues in diagnosis and treatment. Hum. Exp. Toxicol. 26, 191–201.
Bhattacharya, R., Vijayaraghavan, R., 2002. Promising role of alpha-ketoglutarate in protecting against the lethal effects of cyanide. Hum. Exp. Toxicol. 21, 297–303.
Edwards, T.J., Maurer, G., Newman, J., Prausnitz, J.M., 1978. Vapor–liquid-equilibria in multicomponent aqueous-solutions of volatile weak electrolytes. AIChE J. 24, 966–976.
Erlandsson, U., 2007. Dödsbränder 2006, Report no: I 99-149 Räddningsverket, Avdelningen för olycksförebyggande arbete, Karlstad.
Hall, A.H., Dart, R., Bogdan, G., 2007. Sodium thiosulfate or hydroxocobalamin for the empiric treatment of cyanide poisoning? Ann. Emerg. Med. 49, 806–813.
Holland, M.A., Kozlowski, L.M., 1986. Clinical features and management of cyanide poisoning. Clin. Pharm. 5, 737–741.
Johanson, G., 1991. Modelling of respiratory exchange of polar solvents. Ann. Occup. Hyg. 35, 323–339.
Karter, Jr., M.J., 2007. Fire loss in the United States during 2006, Report no: 9/07. Fire Analysis and Research Division National Fire Protection Association.
Lundquist, P., Rosling, H., Sörbo, B., 1988. The origin of hydrogen cyanide in breath. Arch. Toxicol. 61, 270–274.
Moriya, F., Hashimoto, Y., 2001. Potential for error when assessing blood cyanide concentrations in fire victims. J. Forensic Sci. 46, 1421–1425.
Moriya, F., Hashimoto, Y., 2003. Chemical factors affecting the interpretation of blood cyanide concentrations in fire victims. Leg. Med. (Tokyo) 1 (Suppl. 5), S113–117.
Musshoff, F., Schmidt, P., Daldrup, T., Madea, B., 2002. Cyanide fatalities: case studies of four suicides and one homicide. Am. J. Forensic Med. Pathol. 23, 315–320.
Mörk, A.K., Johanson, G., 2006. A human physiological model describing acetone kinetics in blood and breath during various levels of physical exercise. Toxicol. Lett. 164, 6–15.
Purser, D.A., 2000. Toxic product yields and hazard assessment for fully enclosed design fires. Polym. Int. 49, 1232–1255.
Roemer, E., Stabbert, R., Rustemeier, K., Veltel, D.J., Meisgen, T.J., Reininghaus, W., Carchman, R.A., Gaworski, C.L., Podraza, K.F., 2004. Chemical composition, cytotoxicity and mutagenicity of smoke from US commercial and reference cigarettes smoked under two sets of machine smoking conditions. Toxicology 195, 31–52.
Schulz, V., 1984. Clinical pharmacokinetics of nitroprusside, cyanide, thiosulphate and thiocyanate. Clin. Pharmacokinet. 9, 239–251.
Simonson, M., Emanuelsson, V., Touvinen, H., 2001. Formation of hydrogen cyanide in fires: a literature and experimental investigation: BRANDFORSK project 510-991. Sveriges provnings och forskningsinstitut (SP), Borås.
Španěl, P., Dryahina, K., Smith, D., 2007a. Acetone, ammonia and hydrogen cyanide in exhaled breath of several volunteers aged 4–83 years. J. Breath Res. 1, L1–L4.
Španěl, P., Dryahina, K., Smith, D., 2007b. The concentration distributions of some metabolites in the exhaled breath of young adults. J. Breath Res. 1, 1–8.
USFA (U.S. Fire Administration), 2007. National Fire Statistics. October 19, 2007 (cited January 14, 2008) (available from: http://www.usfa.dhs.gov/statistics/national/index.shtm).
Vesey, C.J., Cole, P.V., Simpson, P.J., 1976. Cyanide and thiocyanate concentrations following sodium nitroprusside infusion in man. Br. J. Anaesth. 48, 651–660.

English Summary

Numerous people die every year from toxic smoke emitted in fires. Carbon monoxide is thought to be the most important individual factor, the contribution of hydrogen cyanide (HCN) probably being severly underestimated. HCN is emitted from many modern materials when they catch fire, including furniture polstered with polyurethane foam. Cyanide poisoning may alise arise from terrorist attacks and in industrial handling of cyanides. Cyanide poisoning is life threatening and antidote treatment has to be initiated rapidly. At present, however, there is no way of rapid diagnosis of cyanide poisoning.

The long-term goal of this project, partly financed by ÅF, is to develop a rapid method for diagnosis of cyanide poisoning by breath analysis. The project is divided in five steps:

1. Which HCN levels will appear in breath due to washout from the airways, the HCN emanating from high but short and innoxious peaks of HCN in the ambient air? Published paper: *Stamyr K, Nord P, Johanson G. Washout kinetics of inhaled hydrogen cyanide in breath. Toxicol Lett 179 (2008) 59-62* (attached).
2. What are the background levels of HCN in breath from subjcets not exposed to cyanide? Submitted paper: *Background levels of HCN in human breath measured by cavity ring down spectroscopy.*
3. Will HCN in breath increase significantly following systemic intoxication? Partly carried out, manuscript in preparation: *Physiologically-based toxicokinetic and toxicodynamic modelling of cyanide in human breath.*
4. Development of a fast, simple and reliable direct-reading detector for HCN in breath.
5. The relation between HCN in breath and in blood.

The project constitutes a PhD thesis work presently carried out by MSc Kristin Stamyr.