Hydrogen cyanide, sodium cyanide, and potassium cyanide

Health-based recommended occupational exposure limits

Gezondheidsraad **Voorzitter**
Health Council of the Netherlands

Aan de Minister van Sociale Zaken en Werkgelegenheid
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Onderwerp	: Aanbieding adviezen 'Halothane' en 'Hydrogencyanide, sodium cyanide, and potassium cyanide'
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Mijnheer de Minister,

Bij Brief van 3 december, nr DGV/BMO-U-932542, verzocht de Staatssecretaris van Welzijn, Volksgezondheid en Cultuur namens de Minister van Sociale Zaken en Werkgelegenheid de Gezondheidsraad om gezondheidskundige advieswaarden af te leiden ten behoeve van de bescherming van beroepsmatig aan stoffen blootgestelde personen. In dat kader bied ik u hierbij een advies aan over Halothaan en Cyanides. Het is opgesteld door de Commissie WGD van de Gezondheidsraad en beoordeeld door de Beraadsgroep Gezondheid en Omgeving.

Ik heb deze adviezen vandaag aangeboden aan de Staatssecretaris van Sociale Zaken en Werkgelegenheid en ter kennisname gezonden aan de Minister van Volksgezondheid, Welzijn en Sport en de Staatssecretaris van Volkshuisvesting, Ruimtelijke Ordening en Milieubeheer.

Hoogachtend,

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Dutch expert committee on occupational standards,
a committee of the Health Council of the Netherlands

to

the Minister and State Secretary of Social Affairs and Employment

No. 2002/15OSH, The Hague, 29 October 2002

The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is "to advise the government and Parliament on the current level of knowledge with respect to public health issues..." (Section 21, Health Act).

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Samenvatting

1 Vraagstelling

Op verzoek van de minister van Sociale Zaken en Werkgelegenheid beveelt de Gezondheidsraad gezondheidskundige advieswaarden aan voor beroepsmatige blootstelling aan toxische stoffen in lucht op de werkplek. Deze aanbevelingen worden opgesteld door de Commissie WGD van de Raad, de opvolgster van de Werkgroep van Deskundigen. Zij vormen de eerste stap in een drietraps-procedure die moet leiden tot de wettelijke grenswaarden (MAC-waarden).

In het voorliggende rapport bespreekt de commissie de gevolgen van blootstelling aan cyaniden en presenteert zij, indien mogelijk, een gezondheidskundige advieswaarde voor deze stof. De conclusies van de commissie zijn gebaseerd op wetenschappelijke publicaties die vóór juli 2002 zijn verschenen.

2 Fysische en chemische eigenschappen

HCN

Onder normale omstandigheden is HCN een kleurloze vloeistof of kleurloos gas met de karakteristieke geur van bittere amandelen. HCN gas en vloeistof zijn mengbaar met water en oplosbaar in ethanol en ether. Het kook- en smeltpunt van HCN zijn respectievelijk 25.70^{0}C en -13.24^{0}C.

HCN wordt gebruikt als ontsmettings- of desinfectiemiddel, of in chemische syntheses.

NaCN en KCN

Onder normale omstandigheden zijn de zouten NaCN en KCN witte, kristalleine vaste stoffen met een lichte HCN geur. Het smeltpunt van NaCN is 560^0C en van KCN 620-635^0C. KCN is goed oplosbaar in water, ammonia en formamide, en weinig oplosbaar in ethanol and dimethylformamide. NaCN is goed oplosbaar in water en ammonia en slecht weinig oplosbaar in formamide, ethanol, dimethylformamide, methanol, furfural en ether.

Beiden zouten worden gebruik in de extractie en opwerking van goud of zilver uit ertsen, hittebehandeling van metalen en galvanisering.

3 Monitoring

Voor de bepaling van cyanide in de lucht en andere omgeving matrices zijn er diverse gevalideerde methoden. Voor metingen in lucht wordt cyanide aangebracht op filters in een basische oplossing of op Na_2CO_3 . Vervolgens worden de filters in een basische oplossing geëxtraheerd en het cyanide ion gedetecteerd door middel van ion-specifieke elektrode technieken, zichtbaar infrarood spectrometrie, titrimetrische/colorometrische of potentiometrische technieken.

Voor biologische monitoring zijn geen gevalideerde technieken bekend. Ofschoon zowel cyanide als haar meeste belangrijke metaboliet thiocyanaat bepaald kunnen worden in diverse biologische matrices, geven meetwaarden een onbetrouwbare voorspelling van de externe blootstelling van een individu, vanwege de complexe toxicokinetiek van cyanide. Met name geldt dit voor lage, subletale concentraties en vanwege de aanwezigheid van thiocyanide in veel voedingsmiddelen en cyanide in tabaksrook.

4 Huidige Grenswaarden

In Nederland zijn geen wettelijke MAC waarden vastgesteld voor HCN, NaCN en KCN. Wel wordt een bestuurlijke ceiling waarde van 11 mg/m^3 (10 ppm) gehanteerd voor HCN en een MAC-TGG 8 uur van 5 mg/m^3 als CN^- voor totaal cyaniden inclusief NaCN en KCN .

In de VS heeft de Occupational Safety and Health Association (OSHA) een grenswaarde (TGG 8 uur) van 11 mg/m^3 (10 ppm) vastgesteld, zonder een ceiling of TGG 15 min waarde. De ACGIH daarentegen heeft een ceiling waarde van 5 mg/m^3

vastgesteld. Duitsland heeft een grenswaarde van 2.1 mg/m^3 voor HCN en 2 mg/m^3 voor totaal cyaniden vastgesteld. In de meeste landen geldt voor cyaniden een indicatie voor huidopname.

5 Kinetiek

HCN wordt door de mens gemakkelijk in grote hoeveelheden opgenomen na inademing, dermale of orale blootstelling. Dit geldt ook voor de zouten NaCN en KCN mits de zoutdeeltjes of druppels van de zoutoplossingen inhaleerbaar zijn, danwel bevochtigd bij dermale blootstelling. Er vindt vrijwel volledige opname plaats bij orale blootstelling.

Over de distributie van subletale cyanide blootstellingsconcentraties is geen informatie beschikbaar. Bij hogere (bijna) letale blootstellingsconcentraties wordt cyanide terug gevonden in veel weefsels en in het bloed. Relatief hoge concentraties worden gevonden in lever, longen, nieren, hersenen en bloed.

De belangrijkste omzettingsroute van cyaniden is de vorming van thiocyanaten door middel van de opname van sulfaan-sulfur van het thiosulfaat of andere sulfaan-sulfur bevattende verbindingen (transsulfurisatie); het enzym rodanese speelt hierbij een sleutelrol. De snelheidsbeperkende factor in deze route is een tekort aan sulfaan-sulfur verbindingen in het lichaam. Vandaar het gebruik van thiosulfaat als tegengif in het geval van een cyanide vergiftiging.

Cyanide wordt voornamelijk uit het lichaam verwijderd in de vorm van thiocyanaat via de urine bij hoge blootstellingsconcentraties. Andere, minder belangrijke uitscheidingsroutes zijn de uitademing van CO_2 en kleine hoeveelheden HCN.

Het relatieve belang van de diverse omzettings- en uitscheidingsroutes voor subletale blootstellingsconcentraties is onbekend.

6 Effecten

Irritatie en sensibilisatie

Uit humane gegevens blijkt dat HCN en oplossingen van beiden zouten huid-irriterende eigenschappen hebben. Ten aanzien van oog-irriterende of sensibiliserende eigenschappen van de cyaniden zijn geen gegevens gevonden. Diergegevens suggereren irritatie van de ademhalingswegen na inhalatie van HCN.

Toxiciteit na acute blootstelling

De orale en inhalatoire acute toxiciteit van cyaniden in de mens is uitvoerig onderzocht. Blootstelling aan letale of bijna letale concentraties geeft diverse ademhalings, cardiovasculaire en neurologische klachten. Dood voorafgegaan door coma wordt veroorzaakt door ademhalings- en hartstoornissen.

De acute toxiciteit in de mens vertoont een relatief steile dosis-respons curve: blootstelling voor enkele uren aan 20 mg HCN/m^3 geeft slechts geringe effecten, blootstelling aan 120 mg/m^3 daarentegen kan dodelijk zijn. Overleving van acute cyanide vergiftiging kan leiden tot ernstige neurotoxische complicaties (Parkinsonisme en morfologische beschadiging van de hersenen).

Afhankelijk van de diersoort, cyanide verbinding en blootstellingstijd zijn de volgende orale LD_{50}, dermale LD_{50} en inhalatoire LC_{50} waarden gevonden: 0.09-0.15 mmol/kg (2.34-3.90 mg/kg bw as CN), 0.26-0.34 mmol/kg bw (6.76-8.84 mg/kgbw as CN), en 149-455 mg/m^3 (134-410 ppm). Diverse duidelijke ademhalings, cardiovasculaire en neurologische effecten zijn gevonden bij bijna letale concentraties in dieren, vergelijkbaar met die in de mens.

Veel kwantitatieve en mechanistische informatie is beschikbaar over diverse subletale effecten van eenmalige hoge (bijna letale) blootstellingen aan de drie cyanide verbindingen in dieren. Deze informatie is onvoldoende om een dosis-response curve af te leiden. De meeste aandacht in de studies ging uit naar de chemie en morfologie van het zenuwstelsel, gedrag, functie en morfologie van het cardiovasculair systeem, ademhalingsregulatie en het energiemetabolisme.

Toxiciteit na kortdurende en langdurende blootstelling

Sommige patiënten studies suggereren dat cyanide toxiciteit niet uitsluitend bestaat uit acute effecten en hun gevolgen, maar dat de effecten zich verder ontwikkelen na herhaalde blootstelling, met name neurotoxiciteit en de ontwikkeling van een kropgezwel. Het is echter niet mogelijk deze effecten aan blootstellingsniveau's te koppelen.

Een epidemiologische studie geeft verhoogde incidenties van de volgende symptomen in werknemers die langdurend zijn blootgesteld aan cyaniden in vergelijking met niet-blootgestelde werknemers: hoofdpijn, verzwakking, veranderingen in smaak en geur, duizeligheid, irritatie van de keel, overgeven, kortademigheid, tranenvloed, pijn in de hartstreek, kwijlen, verstoring van de scherpstelling en krankzinnigheid. Bovendien wordt een vergrote schildklier gevonden in de meeste van de blootgestelde werknemers, hetgeen duidt op de ontwikkeling van

een kropgezwel. Cyanide concentraties in de lucht (ademzone monsters) varieerden van 4.2 tot 12.4 ppm (4.7-13.9 mg/m^3) als CN^-.

Herhaalde blootstelling van honden aan concentraties van 50 mg/m^3 veroorzaakte ernstige histologische afwijkingen in de hersenen.

Geen histologische effecten op hart, longen and omliggende bloedvaten zijn waargenomen in konijnen die 4 weken werden blootgesteld aan 0.5 mg/m^3 HCN.

Na kortdurende orale blootstelling van dieren werden o.a. effecten waargenomen op schildklier, centrale zenuwstelsel, gedrag, glucose metabolisme, selenium metabolisme, glutation-peroxidase activiteit, adenosine trifosfatase activiteit en mannelijke reproductie organen. Effecten op het gedrag, het centrale zenuwstelsel en de mannelijke reproductie organen werden reeds waargenomen bij de laagst gedoseerde concentraties van 0.4 mg KCN (varken), 0.5 mg NaCN (hond) en 3 mg NaCN/kg bw/per day (rat) , respectievelijk.

In de enige beschikbare langdurende studie, een 2 jaar orale studie met HCN concentraties tot ca 3.5 mg/kg bw/dag in de rat, werden geen nadelige effecten gevonden.

Carcinogeniteit

Een langdurende en enkele ‘langer’ kortdurende studies geven geen duidelijke indicatie van de carcinogeniteit van cyaniden. De opzet van de studies sluit een definitieve conclusie echter uit.

Genotoxiciteit

Op basis van de beschikbare studies lijken de drie cyaniden niet genotoxisch; vanwege het beperkt aantal studies kunnen echter geen definitieve conclusies worden getrokken.

Reproductie toxiciteit

Cyaniden veroorzaken schade aan het embryo en aangeboren afwijkingen bij concentraties die tevens toxisch zijn voor de moeder. Effecten van lagere concentraties ontbreken. Er zijn onvoldoende gegevens over de effecten van cyaniden op de reproductie capaciteit.

Kritische effecten

Het meest belangrijke kritische effect van cyaniden is remming van het enzym cytochroom C oxidase in de ademhalingsketen. Hierdoor blokkeert het zuurstofgebruik

en de productie van adenosine 5'-trifosfaat (ATP) via de oxidatieve fosforylering. Cyaniden kunnen ook andere metallo enzymen remmen, echter deze effecten worden overschaduwd door de effecten van de remming van cytochroom C oxydase, in elk geval bij hoge concentraties.

Cyanide heeft schildkliervergrotende eigenschappen door de vorming van thiocyanaat, die de jodium opname van de schildklier remt.

7 Evaluatie, advieswaarde en huid notatie

Op basis van de informatie over de toxiciteit van cyaniden concludeert de Commissie WGD dat er twee soorten effecten optreden die worden veroorzaakt door verschillende werkingsmechanismen: acute en chronische effecten.

De acute effecten in de mens geven een steile dosis-respons curve: geringe effecten treden op bij lage concentraties van 20-40 mg/m^3, hoge concentraties van 120 mg/m^3 daarentegen kunnen letaal zijn. Dood voorafgegaan door coma wordt veroorzaakt door ademhalings- en hartstoornissen, die het directe resultaat zijn van de remming van cytochroom C oxidase. Diverse ademhalings, cardiovasculaire en neurologische effecten worden gevonden in (bijna) letale concentraties in proefdieren, vergelijkbaar met die gevonden in de mens. Echter uit deze proefdier gegevens kan geen dosis-respons relatie worden afgeleid.

Op basis van deze gegevens maakt de commissie op dat de acuut humane effecten (dood), de meest gevoelige effecten zijn als gevolg van kortdurende cyaniden blootstelling. De steile dosis-respons curve en de ernst van de effecten pleiten ervoor dat het blootstellingsniveau niet overschreden wordt, zelfs niet voor een korte periode. Daarom stelt de commissie voor een ceiling waarde vast te stellen voor de acuut humane effecten. Het laagst-waargenomen-nadelige-effect- niveau (LOAEL) voor de mens is 20 mg/m^3. Op basis van de steile dosis-respons curve en de ernst van de effecten vindt de commissie een onzekerheidsfactor van 2 voldoende voor de extrapolatie van een LOAEL naar een geen-nadelig-effect-niveau (NAEL) zodat de commissie een ceiling waarde van 10 mg/m^3 (9 ppm) voor HCN aanbeveelt.

Volgens de commissie is er geen reden aan te nemen dat er verschillen zijn tussen de acute toxiciteit van HCN, NaCN en KCN. Dit impliceert dat een ceiling waarde voor de zouten direct afgeleid kan worden van de hierboven vastgestelde HCN ceiling waarde. Dit geeft een ceiling waarde van 18 mg/m^3 voor NaCN en 24 mg/m^3 voor KCN, beiden als inhaleerbaar stof.

Vanwege dezelfde effectieve component (het cyanide ion) in de drie stoffen beveelt de commissie een ceiling waarde van 10 mg/m^3 als CN^- aan voor elke combinatie van de drie stoffen.

In een epidemiologische studie met cyanide concentraties van 4.2-12.4 ppm (4.7-13.9 mg/m^3) worden de volgende effecten van langdurende cyanide blootstelling gevonden: hoofdpijn, verzwakking, veranderingen in smaak en geur, duizeligheid, irritatie van de keel, overgeven, kortademigheid, tranenvloed, pijn in de hartstreek, kwijlen, verstoring van de scherpstelling en krankzinnigheid. Bovendien wordt een vergrote schildklier gevonden in de meeste van de blootgestelde werknemers, duidend op ontwikkeling van een kropgezwel. In kortdurende studies in proefdieren, zijn effecten op gedrag, het centrale zenuw stelsel en mannelijke reproductieorganen gevonden bij concentraties van 0.4 mg KCN, 0.5 mg NaCN een 3 mg NaCN per kg bw per day. De enige chronische proefdierstudie in rat geeft geen ongewenste effecten tot 3.5 mg/kgbw/day HCN. De commissie vindt de dierexperimentele gegevens onvoldoende om een gezondheidskundige advieswaarde af te leiden. Uit de humane gegevens maakt de commissie op dat de effecten op de ontwikkeling van een kropgezwel de meeste gevoelige effecten zijn van langdurende cyanide blootstelling.

De LOAEL voor langdurende blootstelling aan cyanide is 4.2 ppm (4.7 mg/m^3). Omdat er geen dosis-respons relatie is gezien in de studie stelt de commissie een onzekerheidsfactor van 5 voor de extrapolatie van LOAEL naar NAEL voor. Met in achtneming van deze onzekerheidsfactor van 5 beveelt de commissie een gezondheidskundige advieswaarde aan voor cyanide van 1 mg/m^3 (0.9 ppm), gemiddeld over een achturige werkdag.

De gezondheidskundige advieswaarden voor NaCN en KCN kunnen vervolgens berekend worden als 1.8 en 2.4 mg/m^3 respectievelijk, gemiddeld over een achturige werkdag, als inhaleerbaar stof.

Vanwege de vergelijkbare effectieve component (het cyanide ion) in de drie stoffen beveelt de commissie een gezondheidskundige advieswaarde van 1 mg/m^3 as CN^- aan voor elke combinatie van de drie stoffen.

Vanwege de zeer goede doorlaatbaarheid van de huid van HCN en cyanide anionen in waterige oplossing, stelt de commissie een huidnotatie voor, voor alle drie de stoffen.

Executive summary

1 Scope

At the request of the Minister of Social Affairs and Employment, the Health Council of the Netherlands recommends health-based occupational exposure limits for the concentration of toxic substances in the air at workplaces. These recommendations are made by the Council's Dutch Expert Committee on Occupational Standards (DECOS). It constitutes a first step in a three-step procedure that leads to legally-binding limit values.

In the present report the committee discusses the consequences of occupational exposure to hydrogen cyanide (HCN), sodium cyanide (NaCN), and potassium cyanide (KCN). The committee's conclusions are based on scientific publications prior to July 2002.

2 Physical and chemical properties and use

HCN

At ambient conditions, HCN is a colourless liquid or a colourless gas with the characteristic odour of bitter almonds. Gas and liquid are miscible with water and soluble in ethanol and ether. At atmospheric pressure the boiling and melting points of HCN are 25.70°C and -13.24°C, respectively.

The compound is used as a fumigant or desinfectant, and as a precursor in chemical syntheses.

NaCN and KCN

At ambient conditions, NaCN and KCN are white crystalline solids, with a slight HCN odour. The melting points are about 560ºC and about 620-635ºC at ambient atmospheric pressure for NaCN and KCN, respectively. KCN salt is readily soluble in water, ammonia and formamide, and slightly soluble in ethanol, dimethylformamide; whereas NaCN is readily soluble in water, ammonia en slightly soluble in formamide, ethanol, dimethylformamide, methanol, furfural and ether.

Both salts are used in the extraction and recovery of gold and silver from ores, the heat treatment of metals, and electroplating. Furthermore, they serve as precursors in chemical syntheses.

3 Monitoring

Various validated methods exist for the determination of cyanide in ambient air and other environmental matrices. In case of ambient air, cyanide is trapped on filters, in a basic solution, or on Na_2CO_3. Subsequent extraction from filters is carried out with a basic solution. The cyanid ion is detected by means of a ion-specific electrode technique, visible/infra red spectrometry, titrimetric/colorimetric techniques, or a potentiometric technique.

No validated methods for biological monitoring are available. Although, cyanide as well as its most important metabolite thiocyanate can be determined in various biological matrices, the complexity of cyanide toxicokinetics makes these concentrations rather unreliable predictors of external exposure on the individual level, in particular in case of low, clearly sublethal levels, and even more so, because of the occurrence of thiocyanide in many foodstuffs and cyanide in tobacco smoke.

4 Current limit values

No occupational exposure limits (OELs) have been established for HCN, NaCN and KCN in the Netherlands. A ceiling value of 11 mg/m^3 (10 ppm) is presently being used as administrative force for HCN. Furthermore, a OEL, 8 h TWA for total cyanides, including NaCN and KCN of 5 mg/m^3 as CN^- is maintained.

The OEL established by the Occupational Safety and Health Association (OSHA) in the USA is 11 mg HCN/m^3 (10 ppm), 8 h TWA (permissible exposure limit (PEL), final rule limit), without an additional ceiling level or short-term exposure limit

(STEL), while the threshold limit value (TLV) for HCN established by the American Conference of Governmental Industrial Hygienists (ACGIH) amounts to a ceiling value of 5 mg/m^3. The Deutsche Forschungsgemeinschaft (DFG) has established an OEL of 2.1 mg/m^3 for HCN and 2 mg/m^3 for total cyanides. In most countries skin notations exist.

5 Kinetics

HCN is readily and largely absorbed by humans after inhalation, dermal and oral exposure. The same holds for the two salts, provided that particles of the salts or droplets of solutions of the salts are inhalable in case of inhalation, while the presence of moist is a prerequisite for efficient dermal absorption. Oral absorption of the salts can be regarded as virtually complete.

No information is available on the distribution of low, clearly sublethal doses of the three compounds. In case of lethal or nearly lethal doses, cyanide is found in many tissues and in the blood. Relatively high concentrations are encountered in liver, lungs, kidneys, brain and blood.

Various biotransformation pathways have been identified for cyanides, the most important being the formation of thiocyanate by the acceptance of a sulphane-sulphur of thiosulphate or other sulphane-sulphur containing compounds (transsulphurization), the key enzyme being rhodanese. The rate limiting factor of this pathway is the lack of sulphane-sulphur sources in the body. Hence the use of thiosulphate as an antidote in case of cyanide poisoning.

Cyanide is largely eliminated from the body via the urine in the form of thiocyanate in case of high exposure levels. Other, minor elimination routes exist, including the exhalation of carbon dioxide and traces of hydrogen cyanide.

The relative importance of the various biotransformation and elimination routes is unknown for lower, clearly sublethal exposure levels.

6 Effects

Irritation and sensitisation

Human data show that HCN and solutions of the two salts have skin-irritating properties. No data have been located on the eye-irritating and sensitising properties of the three compounds. Animal data suggest irritation of the respiratory tract after inhalation of HCN.

Toxicity due to acute exposure

Ample information is available about the oral and respiratory acute toxicity of the three compounds in humans. Exposure to lethal or nearly lethal doses leads to a series of respiratory, cardio-vascular and neurological symptoms. Death is preceded by coma and caused by respiratory failure or cardiac arrest.

Acute toxicity in humans shows a rather steep dose-response relationship: whereas exposure for several hours to 20 mg HCN/m^3 leads only to slight effects, exposure to 120 mg HCN/m^3 may be fatal. The survival of serious acute cyanide poisoning may lead to severe neurotoxicological sequelae (Parkinsonism and morphological damage in the brain).

Depending on species, compound and exposure time, the following ranges were found for oral LD_{50} values, dermal LD_{50} values and respiratory LC_{50} values respectively: 0.09-0.15 mmol/kg bw (2.34-3.90 mg/kg bw as CN), 0.26-0.34 mmol/kg bw (6.76-8.84 mg/kg bw as CN), and 149-455 mg/m^3 (134-410 ppm). Various overt respiratory, cardio-vascular and neurological effects were seen at (nearly) lethal levels in animals, comparable to those observed in humans.

Much qualitative and mechanistic information is available on various sublethal effects of single high doses (approaching lethality) of the three compounds in experimental animals. This information does not allow the establishment of dose-response relationships. Attention was, among other endpoints, focused on chemistry and morphology of the central nervous system, behaviour, function and morphology of the cardiovascular system, regulation of respiration, and energy metabolism. Various effects were found on these endpoints.

Toxicity due to short-term and long-term exposure

Some case studies suggest that human cyanide toxicity is not restricted to acute effects and their sequelae, but that effects may gradually develop upon repeated exposure, in particular neurotoxicity and goitre. However, it is not possible to link these effects to exposure levels.

One epidemiological study shows higher incidences of the following symptoms in workers chronically exposed to cyanides, compared to workers supposedly not exposed to these compounds: headache, weakness, changes in taste and smell, giddiness, irritation of throat, vomiting, dyspnoea, lachrimation, precordial pain, salivation, disturbances of accommodation and psychosis. In addition, enlarged thyroids were found in most of the exposed workers, pointing to goitre. Cyanide air concentrations (breathing-zone samples) in this study varied from 4.2 to 12.4 ppm (4.7-13.9 mg/m^3 as CN^-).

Repeated respiratory exposure of dogs to acutely toxic doses of HCN (50 mg/m^3) has been found to result in severe histological lesions in the brain.

No histological effects on heart, lungs, and adjacent arteries were observed in rabbits exposed for four weeks to 0.5 mg/m^3 HCN.

After short-term oral exposure various effects have been observed in experimental animals, among them effects on the thyroid, the central nervous system, behaviour, glucose metabolism, selenium metabolism, glutathione-peroxidase activity, adenosine triphosphatase activity, and male reproductive organs. Effects on behaviour, the central nervous system and male reproductive organs were already observed at the lowest applied doses of 0.4 mg KCN, 0.5 mg NaCN, and 3 mg NaCN/kg bw/per day, respectively.

The sole available long-term study did not reveal effects of HCN in rats after two years of oral exposure to up to about 3.5 mg/kg bw/day.

Carcinogenicity

Although one long-term study and 'longer' short-term studies did not reveal clear signs of carcinogenicity, the set-up of the studies precludes a definitive conclusion.

Genotoxicity

The available studies suggest the three cyanides to have no genotoxic effects. However, in view of the limited range of tests employed, no definitive conclusions are possible.

Reproduction toxicity

Cyanides are embryotoxic and teratogenic at maternally toxic doses. Data for lower doses are lacking. No adequate data about the effects on reproductive capacity are available.

Primary effects

The most important primary effect of cyanide itself is the inhibition of the enzyme cytochrome C oxidase in the respiratory chain, thus blocking the utilisation of oxygen and the production of adenosine 5'-triphosphate (ATP) by oxidative phosphorylation. Cyanides can inhibit other metallo enzymes as well, however, the effects of this inhibition are assumed to be overshadowed by the effects of the inhibition of cytochrome C oxidase, at least at the high dose levels investigated.

Furthermore, cyanide has goitrogenic properties through the formation of the detoxification product thiocyanate, which inhibits the iodine uptake by the thyroid.

7 Health-based recommended occupational exposure limits and skin notation

Based on the information on the toxicity of cyanides, the committee is of the opinion that this clearly points to two groups of effects caused by different mechanisms: acute and chronic effects.

The well-known acute effects in humans show a rather steep dose-response relationship. Whereas slight effects occur at low exposure levels of 20-40 mg/m^3, levels of 120 mg/m^3 may be fatal. Death is preceded by coma and caused by respiratory failure or cardiac arrest which are the direct result of the inhibition of cytochrome C oxidase. Various overt respiratory, cardio-vascular and neurological effects were seen at (nearly) lethal levels in animals, comparable to those observed in humans, however, this information does not allow the establishment of a dose-response relationship.

According to the committee, the acute human data show the most sensitive effect, i.e. death. The steepness of the dose-response relationship and the severity of the acute effects in humans imply at the same time that utmost care should be taken to prevent this exposure level from being exceeded, not even for a short time. Therefore, the commission proposes to assess a ceiling value for the acute health effects of HCN.

Starting from the lowest-observed-adverse-effect-level (LOAEL) of 20 mg/m^3 and in view of the steep overall dose-response relationship and the severity of the acute cyanide toxicity in humans, the committee considers an assessment factor of 2 sufficient for extrapolation from a LOAEL to a no-adverse-effect-level (NAEL) which results in a ceiling value of 10 mg/m^3 (9 ppm) for HCN.

This is further motivated by the fact that the survival of overt acute toxicity may be accompanied by irreversible damage in the brain.

There is no reason for the committee to assume differences in acute toxicity between HCN, NaCN and KCN. This implies, that a ceiling for the salts can be derived directly from the ceiling established hereabove for HCN. This leads to a ceiling of 18 mg/m^3 for NaCN and 24 mg/m^3 for KCN, both as inhalable dust.

In view of the comparability of the three compounds as regards the ultimately effective agent (i.e. the cyanide anion), the committee establishes a ceiling of 10 mg/m^3 as CN^- from any combination of the three compounds.

In an epidemiological study where cyanide air concentrations varied from 4.2-12.4 ppm (4.7-13.9 mg/m^3), the effects of repeated cyanide exposure observed are headache, weakness, changes in taste and smell, giddiness, irritation of throat, vomiting, effort dyspnoea, lachrymation, precordial pain, salivation, disturbances of accommodation and psychosis. In addition, enlarged thyroids were found in most of the cyanide exposed workers, pointing to goitre. In short term studies in experimental animals, effects on behaviour, the central nervous system and male reproductive organs were already observed at the lowest applied doses of 0.4 mg KCN, 0.5 mg NaCN and 3 mg NaCN per kg bw per day, respectively. The sole long-term study in rat did not reveal effects of HCN to up to about 3.5 mg/kg bw/day. The committee considered the animals data as inadequate to serve as a basis for an HBR-OEL for effects on longer-term exposure. According to the committee the human data show that the most sensitive chronic effect of cyanide is the development of goitre.

The committee takes as starting point for deriving a HBR-OEL the lowest-observed-adverse-effect-level (LOAEL) of 4.2 ppm (4.7 mg/m^3). Due to the effects observed in the exposed population at 4.2 ppm and the absence of a dose-response relationship observed in the study, the commission recommends using a factor of 5 for the extrapolation from LOAEL to NAEL. By applying this assessment factor, the committee recommends a HBR-OEL for longer-term toxicity of 1 mg/m^3 (0.9 ppm). This HBR-OEL for HCN represent a time-weighted average over a working day of 8 hour. The respective HBR-OELs for NaCN and KCN can be calculated as 1.8 and 2.4 mg/m^3, 8 h TWA, as inhalable dust.

In view of the comparability of the three compounds as regards the ultimately effective agent (i.e. the cyanide anion), the committee establishes an HBR-OEL 8 h TWA of 1 mg/m^3 as CN^- from any combination of the three compounds.

Based on the very high skin permeability measured for HCN and cyanide anions in aqueous solutions, the committee recommends a skin notation for all three compounds.

Chapter 1

Scope

1.1 Background

In the Netherlands, occupational exposure limits for chemical substances are set, using a three-step procedure. In the first step a scientific evaluation of the data on the toxicity of the substance is made by the Dutch Expert Committee on Occupational Standards (DECOS), a committee of the Health Council of the Netherlands, on request of the Minister of Social Affairs and Employment (Annex A). This evaluation should lead to a health-based recommended exposure limit for the concentration of the substance in air. Such an exposure limit cannot be derived, if sufficient data are not available, or if the toxic action cannot be evaluated using a threshold model. In the latter case an exposure-response relationship is recommended for use in regulatory standard setting.

In the next phase of the three-step procedure, the Social and Economic Council advises the Minister on the feasibility of using the health-based value as a regulatory Occupational Exposure Limit (OEL) or recommends a different OEL. In the final step of the procedure, the Minister of Social Affairs and Employment sets the legal Occupational Exposure Limit.

1.2 Committee and procedure

The present document contains the assessment by DECOS, hereafter called the committee, of the health hazard of hydrogen cyanide, potassium cyanide, and sodium cyanide. The members of the committee are listed in Annex B. The first draft of this

report was prepared by dr W.K. de Raat and C.M.M.G. Vervoort, from the Department of Occupational Toxicology of the TNO Nutrition and Food Research Institute, Zeist, The Netherlands, by contract with the Ministry of Social Affairs and Employment. In November 1999 the president of the Health Council released a draft of the report for public review. The individuals and organisations that commented on the draft are listed in Annex C. The committee has taken these comments into account in deciding on the final version of the report.

1.3 Data

Starting points of the literature search on the health effects of exposure to hydrogen cyanide, potassium cyanide, and sodium cyanide are the reviews by ATSDR (ATS97), Ballantyne and Mars (Bal87a), Ballantyne (Bal87b), Baskin *et al*. (Bas87), Bhatt and Linnell (Bha87), D'Mello (DMe87), EPA (EPA92), Hall *et al*. (Hal87), Hartung (Har94), Homan (Hom87), Isom and Johnson (Iso87), Way (Way84), Wilson (Wil87), and Wood (Woo75). Unless otherwise indicated, data were derived from these documents. Data considered to be critical were evaluated by reviewing the original publications. In addition, literature was retrieved from the on-line data bases Medline, starting from 1960, and Toxline, starting from 1990. An additional search has been carried out in February 1996. After this document was completed, a survey was made of the studies published after this date and before July 2002. As these studies did not significantly affect the conclusions of this document, it was not deemed necessary to deal with them further.

Chapter 2

Identity, properties and monitoring

2.1 Identity

Table 2.1 Chemical names, registry numbers, synonyms and structures[a].

chemical name	hydrogen cyanide	sodium cyanide	potassium cyanide
CAS registry number	74-90-8	143-33-9	151-50-8
registered trade name		cyanogran	no data
NIOSH RTECS number	MW6825000	VZT530000	TS8750000
EINECS number	200-821-6	205-599-4	205-792-3
EEC number	006-006-00-x	006-007-00-5	006-007-00-5
EEC labelling	R: 12-26-50/53 S:(1/2-)7/9-16-36/37-38-45-60-61	R: 26/27/28-32-50/53 S: (1/2)-7-28-29-45-60-61	R: 26/27/28-32-50/53 S:(1/2)-7-28-29-45-60-61
synonyms	- hydrocyanic acid, - prussic acid, - formonitrile, - blausäure	- cyanide of sodium, - hydrocyanic acid sodium salt, - white cyanide	- cyanide of potassium, - hydrocyanic acid potassium salt
structure			
abbreviation	HCN	NaCN	KCN

[a] data obtained from ATS97, Bud89, Che94, Har94, Hom87

2.2 Physical and chemical properties

Table 2.2 Physical and chemical properties[a]

name	hydrogen cyanide	sodium cyanide	potassium cyanide
molecular formula	HCN	NaCN	KCN
molecular weight	27.03	49.02	65.11
boiling point	25.70^{0}C	1496^{0}C (extrapolated)	no data
melting point	-13.24^{0}C	563.7^{0}C (100% NaCN) 560^{0}C (98% NaCN)	1.553 (20^{0}C)
specific gravity	0.6884 (20^{0}C)	1.6	1.56 (25^{0}C)
vapour pressure	98.8 kPa (25^{0}C) 107.6 kPa (27.2^{0}C)	133 Pa (817^{0}C)	no data
vapour density	0.947 (31^{0}C)	not applicable	not applicable
flashpoint	-17.8^{0}C (closed cup)	no data	no data
flammability	6 - 41% (100 kPa, 20^{0}C)	no data	no data
solubility in water	miscible with water	readily soluble	readily soluble
solubility in organic solvents	soluble in ethanol, ether	-slightly soluble in formamide, ethanol, methanol, furfural, dimethylformamide, ether; -readily soluble in ammonia	-slightly soluble in ethanol, dimethylformamide; -readily soluble in ammonia, methanol,formamide
physical form	colourless, low viscosity liquid or colourless gas	white crystalline solid	white crystalline solid
odour	characteristic, bitter almond	odourless when dry, emits slight odour of HCN in damp air	similar to that of HCN
odour threshold	1-5 ppm (1-6 mg/m^3 people sensitive to odour) in water: 0.17 ppm w/v (0.19 mg/m^3) in air: 0.58 ppm v/v (0.65 mg/m^3)	no data	no data
conversion factors	1 mg/m^3=0.890 ppm (20^{0}C)	not applicable	not applicable

[a] data from ATS97, Bud89, Che94, Har94, Jen79, Lid94

2.3 Validated analytical methods

2.3.1 Environmental monitoring

NIOSH method 7904

This method is suitable for measuring HCN, KCN, and NaCN for a period of 8 hours. The compounds are adsorbed onto a filter and a midget impinger containing 0.1 N KOH. The filter is extracted with 0.1 N KOH and cyanide is determined both in the filter extract and the impinger solution using a ion-specific electrode technique. The overall precision is 8.1% for HCN and 10.3% for KCN at a range of 5-21 mg/m^3 for HCN and 2.6-10 mg/m^3 for KCN. The limit of detection is 0.0025 mg per sample (sample size 10-180 L). Humid atmosphere and the presence of sulphide, chloride, iodide, bromide, cadmium, zinc, silver, nickel, cuprous iron, or mercury influence the sampling efficiency (ATS97).

NIOSH method 6010

This method is suitable for measuring HCN for a period of 15 minutes. The compound is collected in a tube containing Na_2CO_3 600/200 mg and analysed by visible infrared spectrophotometry. The overall precision is 7.6% at a range of 1.1-300 mg/m^3. The limit of detection is 0.001 mg per sample.

One of the most significant problems in cyanide monitoring is the instability of the collected samples. The recommended method for the storage of cyanide samples is to collect the samples at pH 12-12.5 in closed, dark bottles and store them in a cool, dark place. It is also recommended that the samples be analysed immediately upon collection (ATS97).

Some methods available to analyse cyanide in environmental samples are: ion-chromatography (for air and water), spectrophotometric method (for water and food), titrimetric/colorimetric method (for water, waste water, solid waste and oil waste), and potentiometric method (for water). These and some other analytical methods for determining cyanide in environmental samples are described by the U.S. Agency for Toxic Substances and Disease Registry (ATSDR, ATS97).

2.3.2 *Direct monitoring of air concentrations*

Concentrations of hydrogen cyanide can directly be monitored with special devices. These devices are in particular used for alarming personnel in case concentrations exceed acceptable levels, so as to allow immediate action to be taken.

2.3.3 *Biological monitoring*

No validated methods are available.

Chapter 3

Sources

3.1 Natural occurrence

Cyanogenic glycosides occur naturally in a variety of plant species. They include cassava, bitter almonds, the pits of stone fruits such as cherry, peach and apricot, sorghum, vetch, lima beans, southern mock orange and apple seeds (Hom87). Cyanide itself is not found free in intact plants (Woo75). It is likely that hydrogen cyanide is formed, usually in trace quantities, whenever hydrocarbons are burned in air or when photosynthesis takes place (Jen79). Hydrogen cyanide is also formed during the storage of liquid manure. Concentrations in storage cellars can be so high as to cause acute poisoning or even death in persons descending in the cellars for maintenance work.

3.2 Man-made sources*

3.2.1 Production

HCN

Hydrogen cyanide is manufactured largely by reaction of ammonia, air, and methane in the presence of a platinum catalyst (the Andrussow process):

* Data from ATS97, Har94, and Hom87, unless otherwise indicated.

$$2NH_3 + 2CH_4 + 3O_2 \xrightarrow{1100^0C/Pt} 2HCN + 6H_2O$$

This is the dominant commercial process for direct production of hydrogen cyanide.

The Degussa process is a complex modification of the Andrussow method with higher yields. It is most useful in small scale production where methane is expensive:

$$CH_4 + NH_3 \xrightarrow{1200^0C/Pt\text{-}Al\text{-}Ru} HCN + 3H_2$$

The Shawinagan process requires high energy input, but is useful where methane is not available:

$$3NH_3 + CH_3CH_2CH_3 \xrightarrow{1370^0C} 3HCN + 7H_2$$

In addition, cyanide is produced as a by-product of the synthesis of acrylonitrile from propylene, ammonia and air. Of the total production, 20.5% is produced as a by-product of acrylonitrile production. Direct synthesis, i.e. synthesis directly aimed at cyanide, accounts for the remaining 79.5% .

KCN, NaCN

Almost all sodium and potassium cyanide are produced by the neutralisation or wet process:

$$HCN + NaOH \text{ (or } KOH) \rightarrow NaCN \text{ (or } KCN) + H_2O$$

Purified hydrogen cyanide from the Andrussow and by-product HCN from acrylonitrile processes are used in most commercial NaCN processes. Sodium (and potassium) cyanide can also be prepared by heating sodium (potassium) amide with carbon, by melting sodium chloride and calcium cyanamide together in an electric furnace, or by direct reaction of hydrogen cyanide with caustic soda to form sodium cyanide.

In 1989, about 518,000 tons of cyanide was produced in the U.S.A. This production was projected to grow at approximately 3% per year to 590,000 tons in 1994. The production of hydrogen cyanide in 1977 was 259,000 tons in the U.S.A. World wide annual production and capacity of hydrogen cyanide are estimated to be 500,000 and 590,000 metric tons, respectively. World-wide annual usage and capacity of alkali cyanides (KCN and NaCN among others) are estimated to be 113,000 and 136,000 metric tons, respectively.

3.2.2 *Uses*

HCN

The chief uses of hydrogen cyanide are the fumigation of ships, buildings, orchards, and various foods, in electroplating; for the production of chelating agents such as EDTA, and in metal heat treatment processes. It also has many uses as a chemical intermediate.

According to the ATSDR the use pattern for hydrogen cyanide is the following: for adiponitrile (for nylon) 43%, for methyl methacrylate 33%, sodium cyanide 9%, cyanuric chloride 6%, chelating agents 5%, and miscellaneous uses including methionine and nitriloacetic acid 4% (ATS97). Miscellaneous applications also include the use of hydrogen cyanide as an insecticide and rodenticide (although this kind of use is diminishing) or fumigating enclosed spaces and its use in the manufacture of ferrocyanides, acrylates, lactic acid, pharmaceuticals, and special chemicals.

NaCN, KCN

Some of the most important uses of sodium and potassium cyanide are in the extraction and recovery of gold and silver from ores, the heat-treating of metals, electroplating, various organic reactions, and the manufacture of adiponitrile.

Synthesis of materials from sodium cyanide may constitute as much as 25% of the total use and fall into five general categories: dyes, including optical brighteners; agricultural chemicals; pharmaceuticals; chelating or sequestering agents and specialities. Potassium cyanide is primarily used for fine silver plating, for dyes and speciality products. It is also used with sodium cyanide for nitriding steel and also in mixtures for metal colouring by chemical or electrolytic processes.

Chapter 4

Exposure

4.1 General population

Anthropogenic sources are responsible for most of the cyanide (CN and CN-compounds) in the environment. The major cyanide released to water are discharges from metal finishing industries, iron and steel mills, and organic chemical industries. Vehicle exhaust is the major source of cyanide released into the air. The major source of simple and complex cyanide release to soil appears to be disposal of cyanide wastes in landfills and the use of cyanide-containing road salts (ATS97).

The general population may be exposed to cyanide from inhaling air, ingesting food, and drinking water contaminated with it. Since most of the cyanide in the air will be present as hydrogen cyanide, the primary inhalation exposure to cyanide will occur from hydrogen cyanide. Among the general population, subpopulations with the potential of exposure to cyanide concentrations higher than background levels include cigarette smokers and non smokers who inhale secondary smoke, residents who live near industrial sites releasing cyanide to the environment, residents who live near cyanide-containing hazardous waste sites, and people who consume foods high in cyanogenic glycosides.

Based on an atmospheric hydrogen cyanide concentration of 190.9 ng/m^3 (170 ppt) and an average daily inhalation rate of 20 m^3, the inhalation exposure to hydrogen cyanide is estimated to be 3.8 µg/day. In chlorinated drinking water, cyanide will be present as cyanogen chloride. The mean concentration ranges from 0.45 to 0.8 µg/L. Based on a daily drinking water consumption of 2 L, the daily intake is estimated to be

0.9-1.6 µg/day, which is equivalent to 0.4-0.7 µg of hydrogen cyanide on the basis of molar ratio. The difference between smokers and non-smokers can be quite distinct. Mean thiocyanate levels in plasma were found to be 710 and 196 µg/mL; in saliva 7566 and 2031 µg/mL; and in urine 12.26 and 2.10 mg/24 hours in smokers and non-smokers, respectively.

4.1.1 Air

The concentration of cyanide in the northern hemisphere's nonurban troposphere ranges from 180 - 187 ng/m^3 (160 to 166 ppt) (ATS97).

4.1.2 Food

The cyanide concentration in certain varieties of lima beans can be as high as 3 mg/g although values between 0.10 and 0.17 mg/g are common in U.S. lima beans. Cyanide levels monitored in some foods are as follows: cereal grains and their products 0.001-0.45 µg/g, soy protein products 0.07-0.3 µg/g, and cassava 0.3-2.5 mg/g (0.15 - 40 mg per 100 g of fresh root according to Wood (Woo75)). Human exposure to naturally occurring cyanide in foods in the Unites States is expected to be low (ATS97). One cigarette has been estimated to yield 150 - 300 µg of hydrogen cyanide and 1 mg of acetonitrile (a compound formed during the pyrolysis of burning tobacco) (Woo75). Cyanide levels in mainstream (inhaled) smoke from U.S. commercial cigarettes vary from 10 to 400 µg per cigarette; levels in sidestream smoke vary between 0.6% and 27% of those in mainstream smoke (ATS97).

4.1.3 Water

Cyanide has been detected in waste waters from plating industries at concentrations equal or less than 67,000 mg/L. The mean cyanide concentration in most surface waters is less than 3.5 µg/L, although at some local places concentrations can be higher. Cyanogen chloride is formed in chlorated drinking water due to reaction of humic substances with chloramine formed during chlorination. The median cyanogen chloride concentrations in drinking water ranged from 0.45 to 0.80 µg/L (ATS97).

4.2 Working population

Workers in various occupations may be exposed to cyanide. This includes workers involved in electroplating, metallurgy, pesticide application, firefighting, steel

manufacturing, gas works operations, and metal cleaning. Exposure occurs primarily through inhalation and, less frequently, by skin absorption (ATS97).

During the processes of electroplating and casehardening, hydrogen cyanide gas and air-borne cyanide particulates are produced. Workers in such an atmosphere, especially those who are near the electroplating and heat treatment baths, are exposed to hydrogen cyanide gas and cyanide particulates throughout their work shifts and during the entire period of their employment. Concentrations of hydrogen cyanide and cyanide aerosols in an electroplating and casehardening factory ranged from 0.2 to 0.8 mg/m^3 with a mean value of 0.45 mg/m^3. In the breathing zone of the general workroom atmosphere in the same factory, the concentration ranged from 0.1 to 0.2 mg/m^3 (mean 0.15 mg/m^3) (Cha80). Cyanide concentrations in air in the electroplating sections of three factories ranged from 8.2-12.4, 4.2-8.8, and 5.9-9.6 ppm (9.2-13.9, 4.7-9.9, and 6.6-10.8 mg/m^3) (ElG75). Concentrations of hydrogen cyanide in air in a plating facility of a U.S. airline company ranged from 0.001 to 0.004 mg/m^3, in a work area beside a stripping tank of another plating facility it was 4.3 mg/m^3 and in the breathing zone air of workers in yet another plating facility 1.7 mg/m^3 (ATS97).

Chapter 5

Kinetics

5.1 Absorption

5.1.1 Respiratory

HCN

In 1950, Landahl and Herrman determined the respiratory retention of hydrogen cyanide in human volunteers (Lan50). In case of mouth respiration, a retention 39-77% was found (concentrations in inhaled air were 4-5 mg/m^3 (8 experiments), and 5 and 20 mg/m^3 (2 experiments); measurement started within 1 min after the start of exposure and lasted for 1-3 minutes). No dependence of the results on concentration and measurement schedule was observed. Nasal retention was 13-19% (four experiments).

It is unclear, whether these results represent steady-state respiratory retention. This depends on exposure time, blood/air partition coefficient, tissue/blood partition coefficient, immobilisation of the cyanide due to chemical or physical binding, metabolic clearance and non-respiratory excretion. However, in view of the short duration of exposure, the measured retention percentages have to be regarded as maximum values.

High respiratory absorption of HCN has been assumed by several authors solely based on the physico-chemical properties of the compound (e.g., ATS97, Bon84).

NaCN and KCN

Occupational respiratory exposure may occur to NaCN and KCN in solid form or in dissolved form. In both cases, the actual respiratory absorption will in the first place depend on particle size or droplet size (i.e., aerodynamic diameter; Tas66, ISO83). However, when particles or droplets are indeed inhalable, complete absorption may be assumed, based on the physico-chemical properties of NaCN and KCN. Both compounds dissolve rapidly in water, resulting in alkaline solutions (Bud89, Har94). It can be expected that the small CN^- ions and the small HCN molecules formed in these solutions from the dissolved salts, will readily pass the respiratory membranes.

5.1.2 Dermal

Dugard (Dug87) investigated the penetration of human skin by $Na^{14}CN$ and $H^{14}CN$, using an *in-vitro* system. For aqueous solutions, the CN-absorption rate (or flux) was found to be strongly pH dependent. This was assumed to be the result of the strong pH dependence of the HCN-CN^- ratio in the solution. Based on this assumption, a 30-fold higher flux was established for HCN than for CN^-. The permeability constants for CN^- and HCN when present in an aqueous solution were 3.5×10^{-4} cm/h and 10^{-2} cm/h, respectively. From experiments carried out with vapour-phase HCN, the authors conclude that the same values can be applied for vapour-phase HCN as for dissolved HCN.

The study shows that very high rates of skin absorption can be reached for HCN. In case of the salts, the pH of their aqueous solution is important. However, a permeability constant of 3.5×10^{-4} cm/h can still be regarded as high. So, irrespective of pH, it can be concluded that NaCN and HCN are readily absorbed from aqueous solutions by human skin. This conclusion can safely be extrapolated to KCN.

5.1.3 Oral

Gettler and Baine (Get38) treated three dogs with KCN by gavage and determined the amount of cyanide present in the stomach and intestines after the dogs had died (within 10 to 15 min). From total doses of 100 and 50 mg, 83.4 and 38 mg was recovered in stomach and intestines, respectively, from which the authors concluded that 16.6% and 24% of the administered dose had been absorbed before the dogs died.

Based on elimination of radioactivity via the urine by rats treated with $K^{14}CN$, Farooqui and Ahmed (Far82) found a minimum absorption of 47% over a period of 24 h. A comparable value (45.5%) was found by Crawley and Goddard (Cra77) for a

period of 24 h based on urinary excretion, while the percentage was 94.7%, when the urine was collected over a period of 8-14 days.

A lower minimum absorption estimation was obtained by Leuschner *et al*. (Leu91). These authors gave rats drinking water with cyanide for 13 weeks. Daily doses were calculated to amount to about 0, 40, 80 and 140-160 mg/kg bw. About 11% of the daily dose was excreted via the urine as thiocyanate (the main metabolite of cyanide; see Section 5.3) and only 0.003% as cyanide. So the minimum absorption amounted to 11% in this case of sub-acute oral exposure.

5.2 Distribution

Several studies have been carried out in which cyanide (CN^-) levels were determined in blood and a series of tissues after lethal exposure to HCN, KCN or NaCN via various routes (Ans70, ATS97, Bal83a, Bal83b, Bal87b, Bal88, Bal94, Far82, Get38, Yam79, Yam82). These studies give an impression of the distribution at the time of death or shortly thereafter.

Human cases of oral lethal poisoning have revealed the tissue concentrations listed in Table 5.1.

In one human case of respiratory lethal poisoning, concentrations of 0.75, 0.42, 0.41, and 0.33 mg/100 mg were found in lungs, blood, kidneys, and brain, respectively, while in another case these levels were 0.5, 0.11, 0.7, and 0.3 mg/100 g for blood, kidneys, brain, and liver, respectively (ATS97).

Table 5.1 Mean levels and ranges of cyanide concentrations in human organs in cases of fatal poisoning (Ans70).

matrix	no. of cases	mean (mg %)	range (mg %)
blood	58	2.39	0.0-5.3
brain	34	1.20	0.0-19.9
liver	48	1.62	0.0-25.0
kidney	34	0.61	0.0-2.8
spleen	22	3.77	0.0-37.5
stomach content	49	160.00	0.2-2800
urine	17	0.08	0.0-0.96

As far as can be deduced from Ansell and Lewis, these data are compilated from three other publications, which were not referred to by the committee. It is assumed that the data for the different matrices stem largely from the same cases, as far as these cases were indeed investigated for the presence of cyanide in a certain matrix (Ans70).

Table 5.2 lists the results of a study carried out by Yamamoto *et al*. (Yam82), in which the cyanide distribution was investigated in rats after oral and respiratory exposure to HCN. The respiratory exposure levels cannot be defined.

Table 5.2 Distribution of cyanide in rats after oral and respiratory exposure (Yam82)

	oral 7 mg/kg 10 rats	oral 21 mg/kg 9 rats	respiratory low 12 rats	respiratory high 12 rats
blood (mg/100ml)	0.5	0.48	0.29	0.31
liver (mg/100g)	0.75	1.04	0.22	0.21
lungs (mg/100g)	0.54	0.63	0.48	0.41
spleen (mg/100g)	0.25	0.18	0.06	0.08
brain (mg/100g)	0.13	0.18	0.13	0.16
time to death (min)	10.3	3.3	9.6	5.4

The table lists mean concentrations and times.

The results of Ballantyne (Bal83a) allow the cyanide distributions in rabbits after lethal exposure via various routes to be compared. The distributions were not clearly route dependent, except for a relatively higher concentration in the liver after intraperitoneal and oral exposure, as compared to intramuscular, dermal, ocular, and respiratory exposure. For example, in case of oral exposure, mean liver, kidney, brain, heart, lung, and spleen concentrations were 512, 83, 95, 105, 107 and 72 µg/100 g, respectively, while in case of dermal exposure these concentrations were 26, 66, 97, 110, 120, and 21 µg/100 g, respectively. This difference can be attributed to the fact that, when the first two exposure routes are applied, cyanide is first transported to the liver via the portal vein.

Ballantyne also investigated the species dependence of the distribution (Bal83a). The following species were compared: rabbit, pig, monkey, rat, and sheep. KCN was administered by intraperitoneal injection. A clear species dependence was observed. For example, very high relative liver concentrations were observed in sheep and very low ones in rats.

Obviously, the results presented above are not necessarily applicable to lower, clearly sublethal exposure levels. It may be assumed that the severe toxicity preceding death will influence the distribution. Moreover, detoxification mechanisms may be saturated at lethal doses. However, data on the distribution in experimental animals at lower, sublethal exposure levels are virtually absent.

5.3 Biotransformation

Mammalian biotransformation of cyanide (whether derived from HCN, KCN and NaCN or from other cyanides and cyanogens) has amply been studied. This section is largely based on reviews, supplemented with a detailed examination of a number of key publications.

5.3.1 Biotransformation pathways

An overview of the biotransformation pathways is presented in Fig. 5.1

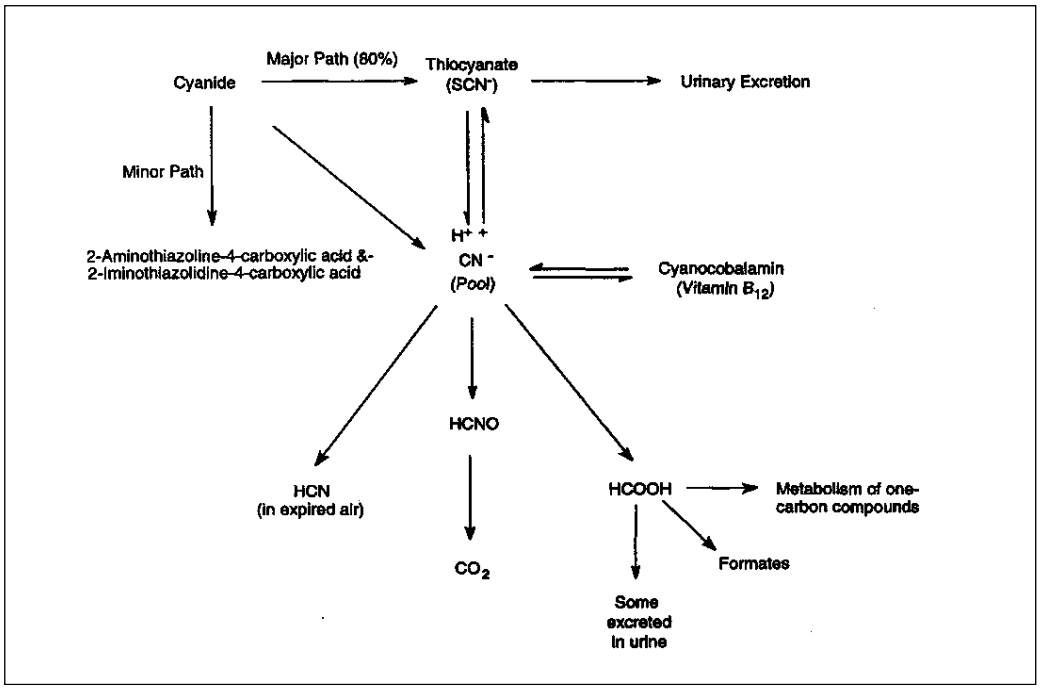

Figure 5.1a Basic processes involved in the metabolism of cyanide in mammals (from ATS97, Ans70).

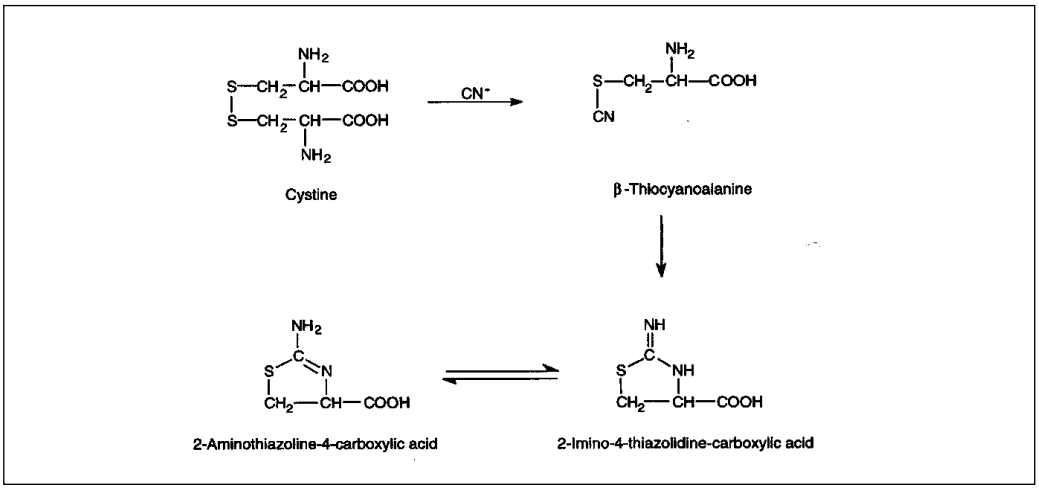

Figure 5.1b Minor path for the removal of cyanide from the body (from ATS97, Ans70).

5.3.2 *Transsulphurization*

Thiocyanate can be formed from cyanide via two pathways, depending on the source of sulphur and the enzyme involved (Wes73, Wes80, Woo75, Wil87). The sulphur may stem from 3-mercaptopyruvate and be transferred to cyanide by the enzyme mercaptopyruvate sulphurtransferase, an irreversible reaction, the mercaptopyruvate being the product of the transamination of cysteine (Wes80).

The second sulphur source consists of the sulphane-sulphur* pool present in the body. Important sulphane-sulphur compounds are thiosulphate, polythionates, thiosulphonates, persulphides, and elemental sulphur in the form of staggered 8-membered rings (Woo75, Way84, Sch69).

It is generally accepted that the enzyme rhodanese (Wes73) directly transfers sulphane-sulphur to cyanide, resulting in thiocyanate. However, an alternative pathway is proposed (Way84, Iso87). According to this pathway, cyanide receives its sulphur in the blood from a serum albumin-sulphane carrier complex without the interference of rhodanese. This complex then receives its sulphane-sulphur from other sulphane-sulphur compounds through the activity of rhodanese.

ATS97 concludes that serum albumin does not play an important role in cyanide detoxification. This conclusion is based on studies in which cyanide lethality was investigated in mice subjected to different feeding regimens, which influenced the serum-albumin levels and rhodanese levels.

* Ionized sulphur bound to another sulphur (Way84).

Another argument against the alternative pathway is provided by Piantadosi and Sylvia (Pia84). These authors found that the replacement of blood in rats by a perfluorochemical emulsion, had no influence on the detoxification of cyanide by thiosulphate, thereby excluding an important role of blood, and thus albumin in the detoxification. Comparable results were obtained by Devlin *et al*. for isolated rat liver and rat hindlimbs (see below) (Dev89).

Irrespective of the existence of the alternative pathway, the key role of rhodanese and sulphane-sulphur compounds in the thiocyanate formation remains undisputed.

The sulphane-sulphur-dependent thiocyanate (SCN^-) formation is essentially an irreversible process* (the reaction between CN^- and $S_2O_3^{2-}$ has an equilibrium constant of 10^{10} (Iso87)), this in contrast to other sulphane-sulphur donor-acceptor reactions catalysed by rhodanese.

The location of rhodanese activity has been extensively investigated, among others, by Himwich and Saunders (Him48, see also Wes73, Woo75, Bha87, Lew91). Rhodanese activity has been detected in virtually all tissues of mammals. In particular, high activities are present in liver and kidneys (Dra87). Muscle tissue may considerably add to the total rhodanese activity, due to its sheer bulk (Dev89). In the cells, rhodanese is located in the mitochondria (Wes73, Koj75).

5.3.3 *Thiocyanate biotransformation*

The biotransformation of thiocyanate in mammals is extensively reviewed by Wood (Woo75). Experiments in which with ^{14}C- and ^{32}S-labelled thiocyanate was administered to rats have revealed the presence of substantial amounts of radioactive carbon dioxide and small amounts of radioactive HCN in exhaled air, while small amounts of radioactive sulphate were excreted via the urine. It was concluded from these experiments that a substantial part of the thiocyanate was converted to cyanide, the carbon of which was largely excreted as carbon dioxide.

Rapid cyanide formation was demonstrated after thiocyanate had been added to human and rabbit blood. Furthermore, cyanide was found in the blood of patients treated with thiocyanate for hypertension. It was shown that cyanide formation in blood was due to the action of a peroxidase in the erythrocytes, which was later identified as haemoglobin. Cyanide formation from thiocyanate has also been found in the salivary glands, the thyroid, and in lymphocytes. The formation of cyanide in the salivary glands and in the thyroid was ascribed to lactoperoxidase and thyroid peroxidase respectively.

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* In the sense that the sulphur in thiocyanate cannot be used by rhodanese for transsulphurization. However, this is not to say that cyanide cannot be formed from thiocyanate (see under '*Thiocyanate biotransformation*').

5.3.4 *The thiocyanate-cyanide cycle*

It has been hypothesised that there exists a thiocyanate-cyanide cycle in mammals (Woo75). Thiocyanate is formed by transsulphurization from cyanide and sulphane-sulphur, catalysed by rhodanese, or from cyanide and mercaptopyruvate, catalysed by mercaptopyruvate sulphurtransferase. Cyanide can again be formed from thiocyanate by peroxidation. The following leaks of the cycle are identified:

- the excretion of cyanide
- the excretion of thiocyanate
- entry of cyanide into the one-carbon pool
- reaction of cyanide with cystine to form β -thiocyanoalanine (see below)
- reaction of cyanide with hydroxocobalamin to cyanocobalamin (see below)
- reaction of cyanide with methaemoglobin to form cyanmethaemoglobin (see below).

5.3.5 *Relative importance of transsulphurization*

It has amply been demonstrated that thiocyanate formation is an important mammalian biotransformation pathway for cyanide, when external doses of the latter compound reach toxic levels. However, the importance of this pathway is unknown, when external cyanide exposure is too low for the occurrence of overt toxic effects (Wil87, Woo75).

The presence of thiocyanate in the body is in itself no prove for external cyanide exposure or the conversion of endogeneously formed cyanide, because thiocyanate and glucosinolates yielding thiocyanates are present in many foodstuffs (Woo75).

Nevertheless, there are indications that thiocyanate is also formed in the absence of external exposure, which can only be explained by the transsulphurization of cyanide (Woo75).

5.3.6 *Capacity, rate and limitation of transsulphurization*

Okoh (Oko83) treated rats with small doses $Na^{14}CN$ (2 x 8.3 μmol, 30 min in between) by subcutaneous injection. Part of the rats had received KCN in their feed for 6 weeks. Within 12 and 24 hrs about 24% and 58% of the total radioactivity had been excreted via the urine respectively. The distribution of this activity over thiocyanate, cyanide, and carbon dioxide is presented in Table 5.3. The high proportion of thiocyanate radioactivity exemplifies the importance of transsulphurization as biotransformation pathway. The rats eliminated 17% and 46% of the total applied radioactivity in the

form of thiocyanate within 12 hrs and 24 hrs, respectively. There is no apparent effect of the oral pretreatment.

Table 5.3 Cumulative distribution of radioactivity in various urine fractions after injection of $Na^{14}CN$ (from Oko83).

KCN in diet (μmol/rat/day)	time after injection (hr)	radioactivity as % of activity in urine		
		SCN^-	CN^-	CO_2
0	12	69.5 (1.7)	1.1 (0.2)	5.0 (0.5)
77	12	70.9 (1.9)	1.1 (0.2)	5.3 (0.3)
0	24	80.3 (2.9)	1.4 (0.1)	5.5 (0.3)
77	24	78.8 (2.0)	1.3 (0.1)	6.2 (0.3)

Values in parentheses signify the SEM.
See text for further explanation.

Leuschner *et al*. (Leu91) found a daily urinary thiocyanate excretion of 11% when rats were treated orally with 40, 80, and 160 mg/kg bw/day KCN. Furthermore, this study clearly indicated that at these dose levels, even after 13 weeks, transsulphurization was not saturated.

Mehta and McGinity (Meh77) treated rats once or twice weekly with KCN via a subcutaneous injection of 5 mg/kg bw. Over a period of 8 weeks, no changes in thiocyanate excretion via urine were observed, which again shows that no saturation of transsulphurization occurs. The same was indicated by the dose dependence of thiocyanate levels.

The capacity of the body to detoxify cyanide by transsulphurization is clearly not limited by rhodanese activity (Woo75). In 1948, Himwich and Saunders (Him48) calculated the amount of rhodanese in dog liver and muscles to be sufficient for the detoxification of 243 and 117 mg/min, respectively.

Furthermore, it has amply been demonstrated that detoxification is greatly stimulated if thiosulphate or other sulphane-sulphur compounds are administered to organisms poisoned with cyanide (Iso87, Bha87), showing that the detoxification is limited by the availability of sulphane-sulphur in stead of rhodanese activity. For example, Sylvester *et al*. (Syl83) found a 30-fold increase of cyanide conversion rate in dogs treated with 1 mg/kg NaCN, when they had a steady-state thiosulphate plasma concentration of 2 mM. In that case, a 50% conversion of cyanide to thiocyanate was observed within 3 min.

Devlin *et al*. (Dev89), investigated cyanide disappearance (extraction) and thiocyanate formation in perfused rat livers and rat hindlimbs. Part of their results is reproduced in Table 5.4.

Table 5.4 Extraction of cyanide and formation of thiocyanate in perfused rat liver and rat hindlimb (Dev89).

thiosulphate concentration (mM)	0	0.1	1
liver			
µmol SCN formed/min/kg liver	4.05 (1.7)	97.67 (14)	122.0 (7)
µmol SCN formed/min total liver	37.2 (16)	792.7 (119)	1148.1 (48)
n	13	3	3
muscle			
µmol SCN formed/min/kg hindlimb	0.01 (0.005)	0.11 (0.11)	4.57 (0.5)
µmol SCN formed/min total muscle	0.38 (0.16)	11.3 (11)	542.0 (65)
n	12	3	5

n is number of perfused tissues
Values in parentheses signify the SEM.
Tissues were perfused with 0.10-0.18 mM KCN.
Perfusion rate: 8.5 ml/min.

The table illustrates the detoxification capacity of liver and muscles at physiological perfusion rates and the effectivity of thiosulphate as antidote.

In addition, it was demonstrated by these authors that, in the presence of thiosulphate, three- and six-fold increases of liver perfusion rate led to proportional increases of the extracted amount of cyanide, which makes clear that the detoxification capacity was in fact higher than observed at the physiological perfusion rate. In case of muscle tissue, the extracted amount did not increase with increasing perfusion rate, which indicates maximum detoxification had been reached at the applied perfusion rate.

According to Devlin *et al*., (Dev89) sulphane-sulphur and rhodanese activity are not the sole limiting factors. The transport of thiosulphate and other sulphane-sulphate compounds from blood to mitochondria, where rhodanese is located, is important as well.

5.3.7 *Reaction with cystine*

Cyanide reacts spontaneously with cystine to form cysteine and β-thiocyanalanine (Woo56). The latter compound tautomerizes to 2-imino-4-thiazolidine-carboxylic acid and 2-aminothiazoline-4-carboxylic acid.

5.3.8 *Reaction with cobalamins*

Cyanide reacts spontaneously with cobalamins to form cyanocobalamin. It is suggested that the entry of cyanide into the body's 1-carbon metabolic pool (see below) occurs via cobalamin binding (Box52a, Wil87).

5.3.9 *Reaction with methaemoglobin*

Cyanide in blood has a strong affinity towards methaemoglobin (Way87, Bri87). The binding occurs very rapidly, as is demonstrated by the rapid recovery from cyanide intoxication after the administration of methaemoglobin or its *in situ* formation by, for instance, treatment with amyl nitrite. Theoretically, 1 g of methaemoglobin can bind approximately 60 μmol cyanide. Schulz calculates from the normal physiological methaemoglobin levels a binding capacity of about 10 mg cyanide (Sch84).

5.3.10 *Entry in the 1-carbon metabolic pool*

When experimental animals are treated with $^{14}CN^-$, a small part of the radioactivity is recovered as $^{14}CO_2$ in the expired air and urine (Box52b, Woo75, Oko83, Joh85). Thus, it is concluded that part of the cyanide enters the 1-carbon metabolic pool of the body. It is supposed that cyanide is directly oxidised to cyanate, which compound is subsequently converted to carbon dioxide. The oxidation to cyanate has sofar only been demonstrated in vitro.

5.4 Elimination

5.4.1 *Respiratory excretion*

Ample evidence exists that a small part of the cyanide is excreted by exhalation (Woo75). The study of Okoh (see details in previous section) showed that about 4.2% of the subcutaneously administered radioactivity ($Na^{14}CN$) was excreted in the exhaled air within 12 hrs; the following 12 hrs added only little radioactivity to this. Between

85 and 90% of the exhaled radioactivity consisted of carbon dioxide, the remaining part being HCN. The presence of non-radioactive cyanide in the feed for 6 weeks had no influence on the results (Oko83).

Burrows *et al*. measured the total radioactivity exhaled by mice treated by subcutaneous injection with 5 mg/kg bw of $Na^{14}CN$. The exhalation of radioactivity was followed over a period of 200 min. The radioactivity reached a peak at 80 min, while hardly any was exhaled anymore at 200 min. Total exhaled radioactivity amounted to 3-4% of the injected radioactivity (Bur82).

Johnson and Isom studied excretion via exhalation in mice given one subcutaneous injection of $K^{14}CN$ (4.6 mg/kg bw). A less marked difference between HCN and CO_2 was found, the excretion percentages being 1.24% and 2.51% respectively, within a period of 3.5 h (Joh85).

The study of Lundquist *et al*. made clear that not all cyanide present in exhaled air stems from cyanide to which the organism has been exposed in first instance. These authors found no correlation between cyanide concentrations in blood en exhaled air in non-exposed human subjects (Lun88). Such a correlation may be expected if the exhaled-air concentrations are solely determined by the blood concentrations. Furthermore, all actual breath concentrations were much higher than the breath concentrations calculated from the whole-blood and plasma concentrations. It is concluded by the authors that most of the cyanide in exhaled air of normal healthy subjects is the result of oxidation of thiocyanate by salivary peroxidase (Lun88) (see Section 5.3).

5.4.2 *Urinary excretion*

Urinary excretion is by far the most important excretion pathway for cyanide in experimental animals and humans (ATS97, Bal87b, Har94, Woo75).

Farooqui and Ahmed studied the urinary excretion by rats of a single oral dose of 5 mg $K^{14}CN$ per kg bw. Within 24 h, 47% of the radioactivity was excreted via the urine. A comparable percentage has been reported by Crawley and Goddard (Cra77), viz. 45%. These authors found the urinary excretion to increase to 94.7% of the applied radioactivity over a period of 8-14 days (Far82).

The study of Okoh revealed urinary excretion of 24% and 57% after 12 h and 24 h respectively when rats were treated by subcutaneous injection with 16.6 µmol $Na^{14}CN$ (814 µg, or 432 µg as CN^-). Chronic oral exposure to 77 µmol KCN/rat/day (5 mg, or 2 mg as CN^-) did not affect the urinary excretion of radioactivity. Table 5.3 shows the distribution of the urinary radioactivity over thiocyanate, cyanide and carbon dioxide. These percentages do not add to 100%, which is most probably the result of other radioactive metabolites being present. Probable candidates to explain this deficit are the

two tautomerization products of β-thiocyanoalanine, which arise from the reaction of cyanide with cystine (see Section 5.3). In any case, the results of Okoh show that, under the prevailing conditions, only small quantities of cyanide are excreted (Oko83).

Leuschner *et al*. treated rats with KCN via their drinking water at nominal doses of 40, 80 and 160 mg/kg bw/day for 13 weeks. After 6 weeks the urinary excretion of thiocyanate amounted to approximately 11% of the calculated daily dose, independent of the dose, while urinary cyanide excretion was as low as approximately 0.003% of the daily dose. Increase of the exposure period to 13 weeks had no effect on these results. No other metabolites were determined (Leu91).

In the study of Burrows *et al*., 7-9% of the radioactivity was excreted in the urine during the period the exhalation of radioactivity was followed. So, this study suggests that urinary excretion is far from complete when respiratory excretion has already decreased to negligible levels (Bur82; see Section 5.4.1).

El Ghawabi *et al*. established the relation between respiratory exposure to cyanide and urinary excretion of thiocyanate in a group of 36 workers divided over 3 factories. They found a rather high correlation (not calculated by the authors, only presented by means of a scatter plot). The daily thiocyanate excretion via urine (mg/day) corresponded with 0.65 times the concentration of cyanide in the air in ppm, measured by personal air sampling (ElG75). Assuming a 8 h respiratory volume of 10 m^3, this means that a respiratory dose of 1 mg cyanide corresponds with a thiocyanate excretion of 0.14 mg, which is equivalent to an excretion of 6%. If we assume a respiratory absorption of 50%, this equals to an excretion of 12% of the cyanide via thiocyanate.

The work of Chandra *et al*. allows a comparison of cyanide and thiocyanate concentrations in blood and urine of smoking and non-smoking exposed workers and controls (Cha80). Their results are listed in Table 5.5.

Table 5.5 Cyanide and thiocyanate concentrations (µg/100 ml) in blood and urine of smoking and non-smoking workers and controls (Cha80).

		workers (n=23)		control (n=20)	
		smokers (n=8)	non-smokers (n=15)	smokers (n=10)	non-smokers (n=10)
blood	CN	56	18	5	3
	CNS	480	420	100	40
urine	CN	6	5	3	2
	CNS	620	570	410	80

The table clearly reveals the marked influence of smoking and occupational exposure on the concentrations and gives an impression of the mean relation between internal

exposure and excretion via the urine. Furthermore, the table confirms the negligible share of cyanide in urinary excretion.

5.4.3 Other excretion routes

Okoh studied the faecal excretion in rats. They found it to amount to 1.31-1.41% within 24 h (Oko83; see detailed description in Sections 5.3, 5.4.1 and 5.4.2). Other quantitative data on faecal excretion and on excretion via other routes have not been located.

5.5 Possibilities for biological monitoring

The concentrations of cyanide and thiocyanate in blood and urine can in principle be used as biological markers for exposure to HCN, NaCN, KCN, and other cyanides and cyanogenic compounds.

No systematic investigation into the possibility of biological monitoring based on these concentrations has yet been carried out. Research has either been focused on background concentrations, or on concentrations associated with acute toxic effects; the concentrations associated with chronic toxicity have not received much attention. No biological limit values have been established.

The predictive value of cyanide and thiocyanate concentrations as regards the external exposure on the individual level, will be rather limited. Both concentrations are the resultant of several interdependent toxicokinetic processes. Cyanide will be excreted via urine and exhaled air and it will be formed from thiocyanate by oxidation. Moreover, the concentration of free cyanide in blood will depend on the amounts of methaemoglobin and cobalamin available for binding.

Thiocyanate is formed by two different processes from cyanide (sulphur from mercaptopyruvate and sulphane-sulphur) and subsequently eliminated by urinary excretion, while it may be converted to cyanide again through the activity of peroxidases.

Thiocyanate is not the only possible metabolite. It may be expected that its ‘share’ in the metabolites of cyanide depends both on the individual and on the level of exposure.

Thiocyanate is a component of many food stuffs. High thiocyanate concentrations should, therefore, not directly been interpreted as unambiguous proof for occupational exposure to cyanide. Moreover, the presence of this compound in food stuffs will substantially add to interindividual variation.

Also the presence of cyanide needs not to be taken as proof for external exposure to this compound, as thiocyanate can be oxidated, which process gives rise to cyanide.

Furthermore, smoking can lead to a substantial cyanide exposure, which may obscure cyanide from occupational exposure.

5.6 Summary

- HCN is readily and largely absorbed by humans after respiratory, dermal and oral exposure.
- The cyanide salts NaCN and KCN may be assumed to be readily and completely absorbed by humans after respiratory exposure if the aerodynamic diameter of droplets of their solutions or particles of the salts in dry form falls within the inhalable range.
  Dermal absorption of NaCN and KCN depends on the condition of the skin and the presence of water. Exposure to dry powders of dry intact skin will not result in a substantial penetration. However, exposure of the skin to the salts in dissolved form, or exposure of the moistened skin to dry powders of the salts, will result in substantial absorption.
  A virtual complete oral absorption can be expected for NaCN and KCN.
- After exposure to lethal levels of HCN, NaCN or KCN, cyanide is found in many tissues and in blood. Relatively high concentrations are encountered in liver, lungs, kidneys, brain and blood. A clear species dependence of distribution has been observed (rabbit, pig, rat, monkey and sheep). After intraperitoneal and oral exposure relatively high concentrations are observed in the liver, while the concentrations in this organ are rather low after dermal, ocular or respiratory exposure. No information is available about the distribution at low, clearly sub-lethal exposure levels.
- Cyanide already present in body fluids of humans not apparently exposed, may stem from the oxidation of thiocyanate which enters the body as food component. Smoking is an important direct source of the cyanide body burden.
- The following biotransformation pathways have been identified for cyanide:
  - spontaneous reaction with cystine to cysteine and β-thiocyanalanine, which compound tautomerizes to 2-imino-4-thiazolidine-carboxylic acid and 2-aminothiazoline-4-carboxylic acid;
  - spontaneous reaction with cobalamins to form cyanocobalamin;
  - spontaneous reaction with methaemoglobin to form cyano-methaemoglobin;
  - entry into the 1-C metabolic pool;
  - oxidation via cyanate to carbon dioxide;
  - formation of thiocyanate from cyanide by acceptance of sulphur from mercaptopyruvate; this reaction is catalysed by mercaptopyruvate transferase;

- formation of thiocyanate from cyanide by acceptance of sulphane-sulphur from thiosulphate and other sulphane-sulphur compounds; this reaction is catalysed by rhodanese.

- The relative importance of the various biotransformation pathways is unknown for lower exposure levels. The formation of thiocyanate is the predominant pathway at higher exposure levels.
- Thiocyanate can be oxidated by peroxidases, resulting in cyanide and thiosulphate.
- Formation of thiocyanate from cyanide by transsulphurization and the formation of cyanide from thiocyanate by oxidation are parts of the so-called thiocyanate-cyanide cycle.
- The transsulphurization capacity of the body is not limited by rhodanese activity, even at high, lethal doses, but by the availability of sulphane-sulphur donors. Furthermore, the transport of sulphane-sulphur and cyanide to the rhodanese in the mitochondria is recognised as a rate-limiting process.
- Thiocyanate formation by the acceptance of sulphane-sulphur occurs throughout the whole body, although the largest amount is formed in the liver.
- Urinary excretion is by far the most important elimination route.
- A few percent of cyanide is excreted via exhalation, within the first hours upon exposure. The exhaled material consists largely of carbon dioxide formed by oxidation, probably via cyanate; trace amounts of hydrogen cyanide are also exhaled.
- It takes several days for a single, relatively high dose of cyanide to be eliminated from the body.
- Exposure to cyanide may in principle be monitored by measuring the concentrations of cyanide and thiosulphate in blood and urine. However, the complexity of cyanide toxicokinetics make these concentrations rather unreliable predictors of external exposure at the individual level, in particular in case of low, clearly sublethal exposure levels. The predictive value is further limited by the occurrence of thiocyanate in many foodstuffs and cyanide in tobacco smoke.

Chapter 6

Effects

6.1 Observations in man

6.1.1 Irritation and sensitisation

Contact of the skin with HCN or solutions of the salts may result in dermatitis and rash according to the Environmental Protection Agency (EPA) (EPA92). Ballantyne attributes the dermatitis caused by contact with cyanide salts to a primary irritant effect, which ‘takes the form of a discrete papular eruption, primarily follicular in distribution, and onycholysis may occur’ (Bal87b).

No data on eye irritation or skin sensitisation in humans have been located.

6.1.2 Toxicity due to acute exposure

The acute toxicity of HCN, KCN and NaCH for humans is well documented. Many cases of intentional (suicide, homicide) and accidental (occupational) poisoning have been described.

Ballantyne mentions the following symptoms of cyanide poisoning: ‘anxiety and excitement; rapid breathing; faintness; weakness; headache (pulsating); constricting sensations in the chest; facial flushing; dyspnoea; nausea, vomiting; diarrhoea; dizziness; drowsiness; confusion; convulsions; incontinence of urine and faeces; coma; respiratory irregularities.’ (Bal87b). Ballantyne states further: ‘With massive doses ....

many of the signs and symptoms listed above may not be seen, and there is a rapid onset of poisoning with convulsions, collapse, coma and death. At the other end of the spectrum, when there is exposure to lower atmospheric concentrations of HCN, ingestion of small amounts of cyanide salts, or contamination of the skin, all of the signs and symptoms may develop in an orderly fashion. An early characteristic feature of acute cyanide poisoning, particularly with smaller doses, is the development of tachypnoea and hyperpnoea, resulting in an increased tidal volume.'

In addition, Ballantyne mentions the following complications of acute cyanide poisoning: rhabdomyolysis, diffuse cerebral oedema, central nervous system degenerative changes, and pulmonary oedema. The brain of deceased victims of cyanide intoxication shows pathological changes in the putamen or the globus pallidus (Bal87b).

6.2 Respiratory exposure to HCN

Table 6.1 Relationship of air cyanide concentrations to expected response (Hal87).

response	concentration	
	mg/m^3	ppm
immediately fatal	300	270
fatal after 10 min	200	181
fatal after 30 min	150	135
fatal after 0.5-1 h or later, or dangerous to life	120-150	110-135
tolerated for 20 min-1 h without immediate or late effects	50-60	45-54
slight symptoms after several hours	20-40	18-36

This table deals only with overt acute effects; sequelae of these effects, or effects of long-term exposure are not taken into account. Nevertheless, it gives an impression of a sort of overall dose-response relation for the acute toxicity of HCN after respiratory exposure. The dose-response relation is quite steep. While concentrations of 20 to 40 mg/m^3 lead only to slight symptoms, concentrations larger than 120 ppm (135 mg/m^3) are fatal. It should be emphasised that Table 6.1 represents crude average exposure estimates, based on various studies. Some case studies show that exposure to as high as 500 mg/m^3 for a few minutes has been sustained (Bal87b, Bon84).

Some additional effects (not all of them acute; some of them based on data obtained with experimental animals) of HCN are listed in Table 6.2. This table represents a selection of a table in EPA92, which was originally compilated by National Institute of Occupational Safety and Health (NIOSH) in 1976.

Table 6.2 Effects of respiratory exposure to HCN in humans (EPA92).

responses	concentration (mg/m^3)
fatal after 30 min	243-528
fatal after 30-60 min	110-264
fatal after 60 min	99
complaints of headache, nausea, vomiting, cardiac symptoms	50
minimal symptoms after several hours of exposure	22-44
no observed effect	0-19 (mean 5.4)
fatigue, headache, body weakness, tremor, pain, nausea	5.5-14.3
headache, weakness, changes in taste and smell, throat irritation, nausea, effort dyspnoea, enlarged thyroids, changes in blood chemistry	4.6-13.6 (mean 8.1)
increases thiocyanate excretion in urine, but to a lesser extent than in cigarette smokers; no other effects noted	2.2-7.8 (mean 5.5)
slight decrease in leukocytic activity of cytochrome oxidase, peroxidase and succinate dehydrogenase after an average of 5.4 years of exposure	0.25
no effects	0.11-0.99
no symptoms after 6 hours	20-40
no serious consequences in 1 min	550
no injury in 1.5 min	413
nausea and difficulty concentrating after 91-second exposure	550-688

Like Table 6.1, Table 6.2 reveals a rather steep dose-response/effect relation.

Oral exposure

It is difficult to estimate the oral lethal doses from human case studies. In most cases, exact information is lacking. Furthermore, doses applied in suicide attempts are often very high, and will in many cases have exceeded the dose necessary for the most rapid and severe effects possible.

Ballantyne (Bal87b) refers to three studies which present exposure ranges which lead to death: HCN, total dose of 50-100 mg; HCN, 0.7-3.5 mg/kg; KCN, total dose of 150-250 mg. Gettler and Baine (Get38) estimated the absorbed dose in four cases of lethal oral poisoning, from cyanide concentrations in tissues. Their results are listed in Table 6.3.

Table 6.3 Internal- and external-exposure data in four cases of lethal cyanide poisoning (Get38).

case no.	body weight (kg)	estimated dose (mg)	amount absorbed (as HCN)		
			total (mg)	mg/kg bw	absorption percentage
1	62.5	1.451	228	3.6	16
2	74.5	557	101	1.4	18
3	50.7	297	58	1.0	20
4	51.0	30	24	0.54	82

In addition to Table 6.3, lethal oral absorptions of 0.7 and 3.3 mg/kg CN^- can be mentioned (Bal87b).

EPA lists the following external lethal doses in a summarising table: HCN: 0.71, 0.5, 0.5-3.5 and 0.86-1.29 mg/kg bw CN^-, and for the salts: 2.9 and 0.71-1.42 mg/kg bw CN^-.

It must be emphasised, that some case studies reveal a remarkable resistance of the exposed persons. Survival of rather high doses, with or without detoxification treatment, has been reported (EPA92, Car88, Ros89, Gra89, Mes91, Val92, Sai94, Ros95, Bor95).

Dermal exposure

Hardly any information is available on the acute dermal toxicity of cyanides in humans. However, it can be expected that dermal exposure to solutions of HCN, KCN or NaCN bring about the same type of acute effects as described for respiratory or oral exposure (see Section 6.2).

The one study summarised by Ballantyne (Bal87b) shows that these effects occurred within 5 min when a hand was accidentally exposed to liquid HCN. This rapid onset of systemic effects is not surprising in view of the high dermal acute toxicity found with experimental animals and the very high dermal absorption rate observed in an *in vitro* study with human skin (see Section 5.1).

EPA mentions an estimation of 100 mg/kg bw for the human dermal LD_{50} of HCN (EPA92).

Neurological sequelae of acute cyanide poisoning

Several case reports show that the survival of serious acute cyanide poisoning can lead to severe neurological sequelae (Uit85, Car88, Ros89, Gra89, Mes91, Val92, Bor95, Ros95). The following symptoms are described: parkinsonism, bradykinesia,

hypomimia, affected speech, dysarthria, akinesia, rigidity, dystonia and apraxia of eye opening. Brain autopsy (one case; died 19 months after poisoning) revealed major destructive changes in the globus pallidus and the putamen. Other (surviving) cases were investigated with computer tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET). Effects are located in putamina, substantia nigra, cerebellum and pallida. PET revealed reduced striatal dopa uptake and reduced glucose metabolism in the putamen and the cortex.

6.2.1 Toxicity due to short-term and long-term exposure

Case studies

A number of occupational case studies are summarised in Table 6.4.

This table needs to be interpreted with caution for the following reasons: 1) The effects listed in this table are not necessarily, or in every case the result of short-term or long-term exposure. Some of them may in reality represent acute toxic effects which do not need short-term or long-term exposure to become manifest; 2) Even in cases, where effects were only observed after a relatively long time, the effects may still have an acute character, as they may be the result of an accidentally high exposure; 3) The link between exposure and effects is not always unambiguous. Exposure to other chemicals cannot always be excluded, while effects may also have another cause than exposure to a chemical; 4) These cases suffer from the limitation that hardly any quantitative information is available about the level of exposure.

However, taken together, and in spite of these limitations, the available occupational case studies suggest that short-term and long-term toxicity may be important in case of cyanide exposure, i.e. exposure levels which do not give rise to acute effects, may become toxic if exposure is repeated or maintained.

Most notable are neurotoxicity and effects on the thyroid (goitre). Furthermore, gastrointestinal symptoms are reported, whereas effects on respiration are generally absent. In addition effects on the skin are mentioned, which are probably related to the irritating properties of cyanides.

Table 6.4 Occupational cases of cyanide poisoning.

exposure conditions	symptoms	ref.
twenty-one-year-old female applying silver coating followed by polishing.	general weakness, severe abdominal pain, vomiting, headache and ataxia.	described in Har50
worker in printing shop exposed to fumes from cyanide bath in which copper plates were placed.	after a year, severe gastrointestinal symptoms and disturbance of the whole nervous system, including the intellect, resulted in complete disability, and death within 2 years of cessation of cyanide exposure.	described in Har50
sixty-eight-year-old male cleaned silver by immersing it in a KCN solution, followed by drying it.	characterised as disease of the primary motor neurons causing the clinical picture of acute anterior poliomyelitis; severe pruritus, brown-red pigmentation of the forearms, vertigo, signs of meningitis, loss of power in the forearms. Improvement after 2 months.	described in Har50
photographic worker working over a sink containing KCN and $FeSO_4$.	numbness, vertigo, weakness, nausea, tachycardia, headache, flushing, gastric distress.	described in Har50
'during the course of exposure to a solution of KCN'.	listlessnes, sleeplessness, lumbar pain, anorexia, nausea, constipation, chills, dysnea, slowed pulse; symptoms decreased after terminating working with cyanide; they recurred again when this work was resumed. with cyanide; they recurred again .	described in Har50
male, employed in gold plating for 20 years.	rash on hands, arms and face, nausea and vomiting, abdominal pain and convulsions, recurring with renewed cyanide exposure, incapacitated by vertigo, muscular cramps, headache, weight loss, and weakness.	described in Har50
male, employed as case hardener for 15 years.	weakness and vertigo caused the worker to fell down, weight loss; had to give up work due to muscle weakness in arms and legs.	described in Har50
several girls exposed to cyanide containing in a fluid shoe cleaner.	general malaise and headaches.	described in Har50
workers keeping their arms in KCN solution during gold extraction.	local rash, slight gidiness, and headache.	described in Har50
fifty-nine-year-old male employed in case hardening for 15 years.	mental confusion, motor aphasia and slurred speach; recurrence of symptoms when work as case hardener was resumed after 15 years of other jobs, including vomiting, abdominal cramps, muscular tremors and thyroid changes.	Har50
thirty-six-year-old male exposed to fumes of case hardening for 5 months.	goitre, nervousness, headache, increased irritability.	Har50
twenty-year-old male working as goldsmith apprentice and cleaning goldware with a KCN solution 5-10 times a day for 4 years.	headaches, general malaise, paresis of left arm and left leg, dilatation of left pupil, left sided hemanopia, enlarged thyroid, 100-120 µg/l blood as CN;	San67

Epidemiological studies

El Ghawabi *et al.* (ElG75) Subjects of this study were 36 male workers from the electroplating sections of three factories and 20 male control workers supposed to be without occupational cyanide exposure. All subjects were non smokers and did not consume certain types of food that are known to contribute to the urinary thiocyanate

concentrations. The subjects were interviewed for their medical and occupational histories. Exposure to cyanides was determined by means of breathing-zone air samples of 15 min during a normal working day. The study concentrated on possible effects on the thyroid. The subjects were given radioactive iodine, and the uptake of radioactivity in the neck region was studied.

In addition to conventional haematological parameters, the radioactivity in the chloroacetic-acid precipitable fraction of the blood (^{131}PBI) was determined, as well as the concentration of cyanhaemoglobin. Finally, urine thiocyanate concentrations were determined.

The following ranges of breathing-zone cyanide concentrations were found: 8.2-12.4 ppm (9.2-13.9 mg/m^3) , 4.2-8.8 ppm (4.7-9.9 mg/m^3) and 5.9-9.6 ppm (6.6-10.8 mg/m^3) for factories A, B and C respectively, the respective means being 10.3, 6.5 and 7.8 ppm (11.6, 7.3 and 8.7 mg/m^3 resp.).

The incidence of symptoms among exposed workers and controls is listed in Table 6.5.

Table 6.5 Incidence of symptoms among exposed workers compared with controls (from EIG75).

symptoms	exposed group		control group	
	no. of cases	%	no. of cases	%
headache	29	81	6	30
weakness	28	78	4	20
changes in taste and smell	28	78	-	-
giddiness	20	56	3	15
irritation of throat	16	44	1	5
vomiting	16	44	1	5
effort dyspnoea	16	44	2	10
lachrymation	9	25	-	-
precordial pain	7	19	1	5
salivation	3	8	-	-
disturbances of accommodation	3	8	-	-
psychosis	2	6	-	-

Twenty exposed subjects had enlarged thyroids. In 16 of these, the thyroids were soft and smooth, while the remaining four were firm and nodular, ‘similar to those seen in lymphadenoid goitre’. The exposed subjects showed much higher concentrations of iodine in the thyroids at 4 h and at 24 h (means at 4 h: 37.7% versus 22.4%, $p<0.001$;

means at 24 h: 48.3% versus 40%, $p<0.001$). No differences in mean blood radioactivity were found.

The workers had significantly higher haemoglobin levels and lymphocyte counts than the controls; 20 workers showed punctate basophilia. Cyanhaemoglobin was only detected in the blood of the workers.

The concentration of thiocyanate in the urine increased towards the middle of the working week and became almost stationary during its last three days. The mean stationary concentrations were strongly correlated with the mean air cyanide concentrations in the second half of the week. The following linear relationship was established: $M = 0.65C$, where M represents the total amount of urine thiocyanate excreted over a period of 24 h in mg and C the cyanide concentration in the air in ppm.

It can be concluded that the subjects from the exposed group show a clearly enhanced incidence of various symptoms associated with cyanide exposure compared to the control group. Although the study does not allow for a definitive attribution of these symptoms to actual cyanide exposure, a causal relationship between exposure and symptoms is deemed highly probable by the committee.

The high incidence of thyroid enlargement in the exposed group points to goitrogenicity by thiocyanate formed from cyanide. That the exposure does indeed lead to thiocyanate exposure is clearly shown by the linear correlation between cyanide exposure and urinary thiocyanate excretion.

Thiocyanate is known to interfere with iodine uptake by the thyroid gland and, as a result, may lead to enlargement of the thyroid.

As no information is provided about dermal and oral exposure (and about measures to prevent these types of exposure), the study does not permit direct conclusions about the quantitative relation between respiratory exposure and effects. If we assume the dermal and oral exposure to be negligible compared to respiratory exposure, it seems that the effects are associated with exposures to 4.2-12.4 ppm (4.7-13.9 mg/m^3). However, in view of the rapid and efficient dermal penetration of HCN and its simple salts (see Chapter 5), this form of exposure may not be neglected.

Chandra *et al.* 1980 (Cha80)

Twenty-three male workers employed in case hardening and electroplating, as well as 20 male workers claimed to be ‘never ... exposed to chemical hazards’, were investigated for the urinary excretion of cyanide and thiocyanate and the presence of these compounds in blood samples. In addition air samples were taken from the breathing zone ‘near the work baths and also from eight strategic points on the shop floor’. It is not clear whether air samples were confined to the exposed group or included also the control group.

The authors state that ‘detailed history, clinical examination and pulmonary function tests were also carried out’; however, the results are not presented in any detail. For this, the authors refer to another publication, which could, however, not be located by the committee. It is merely stated that ‘the workers complained of typical symptoms of poisoning’. Therefore, no conclusion can be drawn about the relationship between cyanide exposure and health effects based on this study.

Furthermore, the study provides detailed data about blood and urinary cyanide and thiocyanate levels. These will not be elaborated upon here.

Blanc *et al.* 1985 (Bla85)

Thirty-six former workers of a silver-reclaiming facility were interviewed with the aid of a questionnaire for symptoms during employment, residual symptoms at the time of the study, and aspects of their work in the facility which determine exposure. In addition, the workers were subjected to physical examinations and laboratory studies.

The facility had been closed since February 1983, because of heavy occupational cyanide exposure. The study started in October 1983. No control group was studied, while “the interviewers were not blinded to job histories when symptom complaints were elicited. .... Selection bias, ..., could not be avoided”. One day after closure, a HCN time weighted average (TWA) concentration (24 h) of 15 ppm (17 mg/m^3) was measured. No air concentrations during plant operations were available, but these were expected to be higher than those measured the day after closure. Exposure could occur through inhalation of HCN and dust with NaCN, through skin contact with cyanide-containing liquids, through skin contact with NaCN and through eating in contaminated areas.

During time of employment there was a high prevalence of symptoms that are consistent with acute cyanide intoxication. Severity indices were established based on point scores. These indices showed a significant exposure dependence, expressed as exposure indices, which were again based on point scores. Severity of symptoms showed an inverse trend with time elapsed since last exposure. A positive, although less clear trend was found for employment time. No relation with alcohol use or cigarette smoking was found. Lower, but still high prevalences of several residual symptoms were found, three of them (rash, bitter or almond taste and headache) showing a significant exposure trend. No palpable thyroid abnormalities, mucosal erosion, or ‘focal neurological deficits’ were found. Mean serum vitamin-B_{12} and serum folate levels were significantly decreased compared with ‘laboratory means’, whereas slight increases of serum triiodothyronine and thyroid-stimulating hormone were found.

It can be concluded that the study unequivocally points to clear cyanide-exposure associated effects during employment. Although no data about cyanide exposure levels during employment are available, the study clearly suggests that these effects are indeed the result of cyanide exposure. Furthermore, the prevalence of residual symptoms suggests that cyanide effects can persist for 7 months after exposure has ended.

The value of the study is limited in the context of the present report, as it is impossible to link the symptoms to quantitative exposure levels. Furthermore, the effect interviewers were not blinded for the exposure histories of the subjects, which is deemed a serious flaw and urges caution in the interpretation of the results.

Hlynczak *et al.* (Hly80a)

Hlynczak *et al*. investigated the effects of respiratory exposure to HCN on the concentrations of a number of metals (calcium, potassium, magnesium, copper, iron, and zinc) in the serum of 32 women.

The women themselves were not working with cyanides. The exposure was due to case hardening and electroplating in adjacent factories. The women were employed in a cable factory. Their physical workload was deemed to be 'leicht bis mittelschwer' (light to intermediate). The control group consisted of 39 female desk workers. It is stated that in composing the control group, attention was paid to 'weitestgehender Übereinstimmung wichtiger Parameter, um die Vergleichbarkeit .... zu gewährleisten' (maximum achievable similarity with respect to important parameters, to ensure .... comparability). However, no details are presented on this important aspect. About the exposure it is stated that the maximum of 5 mg/m^3 is occasionally exceeded up to a factor of 1.5. No information is provided on the cyanide exposure of the control group.

Significant increases of zinc ($p<0.001$), calcium ($p<0.001$) and iron ($p<0.05$) were found in the exposed group. The occurrence of a dose-effect relation could not be investigated due to the fact that no high and low exposure groups were distinguished. This makes it impossible to attribute the difference between the two groups unambiguously to the difference in exposure. Other, occupational factors, may be important, i.e. the result merely indicates that working in the cable factory leads to the differences in women.

However, as is pointed out by the authors, the three metals can be found in enzymes or coenzymes which play important roles in the glycolysis (they mention lactate dehydrogenase (LDH), creatine phosphokinase (CPK), alkaline phosphatase (AP), nicotinamide adenosine dinucleotide (NAD). According to the authors, their enhanced serum concentrations may point to intensivation of glycolytic processes in erythrocytes and muscles. This may be a result of a difference in physical workload or

to a reaction of the inhibition of enzymes containing the metals in question by cyanide. Earlier investigations carried out by the authors (not reviewed by the committee) appear to exclude the physical workload as a cause, which leaves, at least according to the authors, the cyanide exposure as a cause.

The value of the study is furthermore restricted by the absence of any dietary data; it cannot be excluded that the effects found have more to do with a difference in nutritional status between the controls and the exposed.

Hlynczak *et al.* (Hly80b)

In a second study, Hlynczak et al. investigated the effects of respiratory exposure to HCN on the activity of a number of serum enzymes in 38 women. The control group consisted of 20 female desk workers of the same factory. The following enzymes were investigated: ASAT, ALAT, LDH, α-HBDH, CPK and AP. Although not explicitly stated, the women (exposed and controls) were most probably part of the same occupational population as those taking part in the first study (Hly80b). It is not clear whether, and if so, how many women were taking part in both studies. Again, maximum HCN concentrations of 7.5 mg/m^3 were reported.

A very significantly increased LDH activity was measured in the serum of the exposed group, while ASAT activity showed a slight increase. No differences were found for the other enzymes. The authors interpret these results as signs of a compensatory reaction of the body to the interaction of cyanide with these metallo enzymes.

The value of the study is restricted by the absence of any dietary data; it cannot be excluded that the effects found have more to do with a difference in nutritional status between the controls and the exposed.

The reader is further referred to the summary of the first study of Hlynczak et al. The same remarks and restrictions hold for the second study.

6.2.2 Exposure to cyanide via food and medicines (Wil87)

Several neuropathological conditions are attributed to the chronic intake of cyanide-containing food. Well known is tropical ataxic neuropathy (parasthensiae of the feet, numbness in the hands, visual loss, diminished hearing, ataxia) in populations which consume cassava as staple food. Cassava contains linamarin, a glycoside which releases free cyanide after consumption. It is generally accepted (although still not fully proven) that the neuropathological condition is indeed caused by chronic cyanide exposure.

An increased incidence of goitre and cretinism in the tropics, notably in Zaire, is postulated to be a result of a low iodine intake combined with a high cyanide intake from cassava.

Unambiguous proof for the existence of chronic cyanide poisoning (neurological symptoms) is provided by the use of amygdalyn or laetrile, a cyanide-containing glycoside from apricot kernels, as a medicine against cancer.

The relevance of these findings in the context of the present report is, that they strongly indicate that chronic cyanide toxicity exists, not only in the form of thiocyanate mediated goitrogenicity, but also in the form of clear neuropathological conditions. However, it is not possible to draw quantitative conclusions from these findings about the chronic toxicity of HCN, KCN and NaCN, the most important reasons for this being differences in toxicokinetics and exposure routes.

6.3 Animal experiments and in vitro systems

6.3.1 Irritation and sensitisation

No studies were located in which the irritating and sensitising properties of HCN, NaCN or KCN were specifically investigated in experimental animals.

Clear signs of eye irritation have been observed when animals were exposed via the eye to study the acute toxicity of HCN, NaCN or KCN (Bal83b, Bal88).

Matijak-Schaper and Alarie found evidence for respiratory irritation by analysing breath rate and pattern of mice exposed to 20-100 ppm (22-112 mg/m^3) of HCN (Mat82).

No other studies with experimental animals were located which revealed signs of irritation, whereas studies pointing to sensitisation of experimental animals have not at all been located.

6.3.2 Toxicity due to acute exposure

Lethality

A number of LC_{50} and LD_{50} values of HCN, KCN and NaCN are listed in Tables 6.6-6.9. These tables are largely based on the work of Ballantyne (Bal83a, Bal83b, Bal87b, Bal88), supplemented with data from Matijak-Schaper and Alarie (Mat82), Higgins *et al*., 1972 (Hig72), and Ten Berge *et al*. (Ber86).

Table 6.6 Lethality of the three cyanides after oral exposure (Bal87b).

compound	species	sex	condition	LD_{50} (mg/kg/bw)	95% conf. int.	LD_{50} (mmol/ kg bw)
HCN	rabbit	female	unstarved	2.49	2.26- 2.81	0.092
HCN	rat	female	starved	3.62	3.08- 3.87	0.127
HCN	rat	female	unstarved	4.21	3.76- 4.95	0.156
NaCN	rabbit	female	unstarved	5.11	4.62- 5.66	0.104
NaCN	rat	female	starved	5.09	4.26- 5.83	0.104
NaCN	rat	female	unstarved	5.72	5.23- 7.08	0.117
KCN	mouse	male	unstarved	8.50	8.10- 9.00	0.130
KCN	rabbit	female	unstarved	5.82	5.50- 6.31	0.090
KCN	rat	female	starved	9.69	8.60-11.30	0.149
KCN	rat	female	unstarved	7.48	6.68- 8.48	0.115
KCN	rat	male	unstarved	10.00	8.70-11.50	0.150

Table 6.7 Lethality of HCN after respiratory exposure (Bal87b, ATS97).

species	sex	exposure time	LC_{50} (mg/m^3)	95% conf. int.	LC_{50} (ppm)
mouse	male	30 min	176	129- 260	156
	not specified	5 min	363	not specified	323
rabbit	female	45 sec	2.432	2304-2532	2.165
		5 min	409	321- 458	364
		35 min	208	154- 276	185
rat	female	10 sec	3.778	3771-4313	3.362
		1 min	1.129	664-1471	1.004
		5 min	493	372- 661	439
		30 min	173	159- 193	154
		60 min	158	144- 174	140
		30 min	151	141- 164	134
	not specified	5 min	553	443-689	492
cat	not specified	30 min	204	not specified	182
goat	not specified	30 min	461	not specified	410

Table 6.8 Lethality of the three cyanides for rabbits after dermal exposure (Bal94).

compound	form	skin condition	LD_{50} (mg/kg bw)	95% conf. int. (mg/kg bw)	LD_{50} (mmol/kg bw)
HCN		intact	6.90	6.43- 7.52	0.260
NaCN	aq.solution		14.63	13.75-15.35	0.299
KCN			22.33	20.43-24.03	0.344
HCN		abraded	2.34	2.06- 2.61	0.087
NaCN			11.28	9.17-12.67	0.231
KCN			14.29	13.27-15.10	0.220
NaCN	powder	intact, dry	>200		>4.10
		intact, moist	11.83	7.40-18.92	0.243
		abraded	7.35	6.68- 7.81	0.151

Table 6.9 Lethality of the three cyanides for female rabbits after ocular exposure (Bal83b).

compound	solution		powder		solid	
	mg/kg bw	mmol/kg bw	mg/kg bw	mmol/kg bw	mg/kg bw	mmol/kg bw
HCN	1.04	0.039				
NaCN	5.06	0.103			4.47	0.09
KCN	7.87	0.121				
NaCN/kaolin			9.06[a]	0.07		

[a] complete formulation, i.e. including kaolin

Lists of intravenous, subcutaneous and intramuscular LD_{50} values are presented by Ballantyne (Bal87b). Ranges of these values are listed in Table 6.10.

Table 6.10 Lethality of the three cyanides after intravenous, subcutaneous, intraperitoneal and intramuscular exposure (Bal87b).

route	number of values	number of species	number of compounds	range (mmol/kg bw)
intravenous	3	1	3 (HCN, KCN and NaCN	0.02-0.03
subcutaneous	5	2	2 (NaCN and KCN)	0.15-0.18
intraperitoneal	18	4	3 (HCN, KCN and NaCN)	0.06-0.12
intramuscular	8	1	3 (HCN, KCN and NaCN)	0.02-0.06

The table lists ranges of the LD_{50} values obtained with the indicated number of species and compounds.

The species sensitivity as regards lethality was investigated by Barcroft (published in 1931; summarised in EPA92), by measuring the lethal time (i.e. the time span between the start of exposure and death) when the animals were exposed to a HCN concentration of 1000 mg/m^3. The following species were subjected to this exposure: dog, mouse, cat, rabbit, rat, guinea pig, goat and monkey; the respective lethal times were 0.8, 1.0, 1.0, 1.0, 2.0, 2.0, 3.0, and 3.5 minutes.

EPA further points to the marked differences in sensitivity found for the same species by different investigators. They refer to the study of Moss *et al*. (Mos51), which reveals a minimal lethal concentration of 55 mg/m^3 HCN for female rats when exposed less than 20 min, whereas in the study of O'Flaherty and Thomas (OFl82) rats tolerated 4 times 12.5 min exposure to 220 mg/m^3 HCN.

For an extensive discussion on the lethality of inorganic cyanides, the reader is referred to Ballantyne (Bal87b) and EPA (EPA92).

Other effects

Overt clinical effects

When cyanide exposure reaches lethal levels, the following overt clinical effects are observed in experimental animals, irrespective of exposure route (Bal83b, Bal94, EPA92, ATS97): dyspnea, irregular, shallow and gasping breathing, ataxia, tremors, retrocolic spasms, tonic spasms, loss of consciousness, convulsions and asphyxiation.

Acute cyanide toxicity shows a steep dose effect relationship, near lethal dose levels lying rather close to the highest dose levels without apparent effects.

The EPA (EPA92) has listed the overt clinical effects at lethal and nearly lethal doses in a table, part of which is reproduced here in modified form as Table 6.11.

Sub-lethal effects

The sublethal acute effects of cyanide exposure have extensively been studied. In general, these studies were not aimed at the establishment of no adverse effect levels for single or short exposures, but at the identification of the different types of effects which are caused by cyanide and at the elucidation of the mechanisms underlying these effects. They have revealed a rather complete *qualitative* picture of acute cyanide toxicity, but do not provide much information about the actual dose levels which are safe with regard to acute effects and longer-term effects. In most studies a single near-lethal dose was employed, this to ensure a clear manifestation of the effects of interest.

Table 6.11 Overt clinical effects at lethal and near-lethal acute exposures (from EPA92).

route	species	compound	dose		exposure conditions	effects
			mg/kg bw or mg/m^3	mmol/kg or mmol/m^3		
inhalation	dog	HCN	590-700 mg/m^3	21-26 mmol/m^3	1.75-2 min	apneic, comatose or convulsive tremors; 1 dog did not die, but showed apparent full recovery; all other dogs died
inhalation	monkey	HCN	110-172 mg/m^3	4.1-6.4 mmol/m^3	30 min	hyperventilation, loss of consciousness, followed by rapid recovery
dermal	dog	HCN	6500-16,900 mg/m^3	240-625 mmol/m^3	47-180 min; no head exposure, i.e. no respiratory exposure	decreased, labored and irregular respiration; face and threat twitches; bright pink and collapsed lungs; all animals died
dermal	guinea pig	HCN	not quantified		approx. 8 min; exposure by pressing a tube filled with liquid HCN against abdomen	rapid respiration, muscle twitches, and convulsions; all animals died
oral	guinea pig	KCN	8 mg/kg bw	0.12 mmol/kg bw	single dose in sucrose	five animals showed no signs of toxicity; 3 had slight tremors but recovered within 15 min
intraperitoneal	mouse	KCN	1-6 mg/kg bw	0.02-0.09 mmol/kg bw	single dose in water	rapid breathing, agitation, loss of co-ordination, and convulsions; at highest dose 80% survival
subcutaneous	mouse	KCN	10, 12 or 15 mg/kg bw	0.15, 0.18 or 0.23 mmol/kg bw	single dose in saline	dose dependent occurrence of tremors
intravenous	dog	NaCN	1 mg/kg bw	0.02 mg/kg bw	single injection in saline	hyperventilation followed by hyperventilation hypoventilation

Neurotoxicity

The central nervous system has been recognised as an important target for cyanide toxicity (Bur82, Per85, Way84). The overt clinical effects which are observed at lethal doses already clearly suggest neurotoxicity (e.g. ataxia, tremors, retrocolic spasms, tonic spasms, loss of consciousness, convulsions). Furthermore, lethality is consistently accompanied by relatively high cyanide concentrations in the brain (parenchyma as well as blood in intracerebral vessels), irrespective of exposure route or species (Bal87b), which shows that the central nervous system in particular is heavily exposed.

Acute cyanide exposure at nearly lethal levels interferes with various neurochemical processes in the brain, leading to changes of the levels of neurotransmittors (e.g. γ-aminobutyric acid (GABA) and dopamine) and their precursors or metabolites (amino acids such as tyrosine and glutamic acid, L-DOPA, dihydroxyphenylacetic acid, hydroxyindolacetic acid, and homovanillic acid) (Tur62, Per85, Yam89,Yam90, Yam92, Yam93, Bal87b, Cas92, Cas95, Kiu92, Owa80, Leu86). Furthermore, effects on cyclic GMP and intracellular calcium levels were observed (Joh86, Per85).

Clear indications were obtained for lipid peroxidation in the brain as an acute effect of cyanides; calcium appears to be involved in this effect (Joh87). Furthermore, antioxidant defence in the brain appears to be compromised by cyanide, due to the inhibition of various enzymes (Ard89, Ard94).

There is evidence that cyanide stimulates the sympathoadrenal system, which effect is reflected by the increase of epinephrine and norepinephrine levels in plasma induced by cyanide treatment (Kan91).

Electrophysiological effects in the brain, measured as changes in the electro encephalogram, were observed after acute cyanide exposure (Bur73, Pur84).

Acute cyanide exposure leads to clear and reversible changes in the concentrations of high-energy phosphate compounds in the rat brain, including a decrease of ATP levels (Dec84). Moreover, a strong increase of lactate and ADP and a strong decrease of glycogen have been observed in the rat brain (Mac89). Effects on rat-brain energy metabolism are also indicated by the inhibition of cytochrome-c-oxidase and mitochondrial respiration rate (Iso82, Pet93). Brain cytochrome-c-oxidase appears to be much more sensitive than cytochrome-c-oxidase in other tissues.

Acute, near lethal, cyanide exposure leads to a variety of histological lesions in the brain (Hay52, Lev59, Lev67, Hir67, Hir68, Fun84, Mac89).

Motor performance and, possibly cognitive functions, can be impaired as a result of acute cyanide exposure (Dme86, DMe87).

Effects on the brain, in particular their distribution over this organ, are influenced by the effects of cyanide on the perfusion of the brain (Bri76, Bri77, Kli82, Fun84, Bal87b).

Cardiovascular effects

Acute cyanide exposure leads to effects on heart function, e.g. affected heart-beat rate and ECG pattern, to myocardial histological lesions, and an increase of cardiospecific creatinine phosphokinase in the blood (Bas87, Lei50, Suz86, Kra71, Vic85, O'F l82, Kli82).

Effects on respiration

Acute cyanide exposure has marked effects on respiration, which most probably find their origin in effects on the central nervous system as well as on peripheral chemoreceptors (Kli82, Pur84, Lag94a, Lag94b).

Energy metabolism

The effects of acute cyanide exposure on energy metabolism are reflected in acidosis (increase of lactate concentrations), reduced carbon dioxide concentrations, increased oxygen concentration, less difference in the red colour between venous and arterial blood, increased catabolism via the pentose phosphate pathway, decreased catabolism via the Embden-Meyerhof-Parnas pathway and the tricarboxylic acid pathway, increases of blood concentrations of glucose and inorganic phosphate (Bal87b, Iso75, Kat80, Kat83).

*6.3.3 Toxicity due to short-term exposure**

The located short-term (i.e., subacute and semichronic) toxicity studies are summarised in Table 6.12 (See Annex D). As was the case with the acute-toxicity studies, most of the short-term studies were aimed at a restricted number of toxicological endpoints. Furthermore, only one dose level was investigated in most studies, this dose level being fairly high in some of them.**

Only three inhalation studies were located, one with dogs and two with rabbits. The dog study (Val52) was mainly concerned with histological effects in the brain after short exposures (12.5 min) to a concentration (50 mg/m^3 HCN), which gave rise to overt signs of acute toxicity. The periods between the exposures were long enough to allow a recovery from these acute effects for 9 of the 12 dogs; 3 of them died during the study. Severe histological damage was observed in the brain. So, this study shows that repeated respiratory exposure to acutely toxic dose levels may lead to severe brain damage.

The studies with the rabbit (Hug79, EPA92), were carried out at a 100-fold lower dose level (0.5 mg/m^3 HCN), while exposure was maintained continuously for up to 4 weeks at this low level. These studies were solely aimed at the observation of possible histological effects in heart, lung, and adjacent arteries. No effects were found.

Table 6.12 (Annex D) lists 11 short-term oral toxicity tests. They reveal effects on the thyroid (Jac88, Phi79), central nervous system and behaviour (Jac88, Phi79,

* Treatment less than one year.

** I.e., approaching the dose levels which gave rise to overt acute toxicity.

EPA92), glucose metabolism (Jac88), selenium metabolism and glutathione peroxidase activity (Bei84), ATPase activity (Oko94), and male reproductive organs (NTP94). Effects on behaviour, brain and male reproductive organs were already encountered at the lowest dose levels applied, i.e. at 0.4 (KCN; oral pig) 0.5 (NaCN; oral dog) and 3 (NaCN; oral rat) mg/kg bw/day respectively, which means that it is not possible to establish a no observed adverse effect level (NOAEL) for short-term oral exposure.

In two studies, the experimental animals were treated parenterally (intraperitoneally and subcutaneously) (Gal76, Kan94). Effects were a reduced copper content of the liver, reduced adenine nucleotide binding, reduced number of tyrosine-hydroxylase positive cells in the brain, and altered behaviour.

No short-term dermal studies were located.

6.3.4 *Toxicity due to long-term exposure and carcinogenicity*

Only one long-term toxicity study has been located by the committee (How55). It is summarised in Table 6.13.

Table 6.13 Results of an oral long-term toxicity study with HCN (How55).

spec.	doses HCN	exposure regimen	investigated endpoints	effects	experimental limit value
rat	0, 50-100 80-300 mg/kg feed, equal to 2.3-4.6 and 3.75-14 mg/kgbw/day for males and 2.2-4.4 and 3.5-13.1 mg/kgbw/day for females.	groups consisting of 10 male and 10 female weanling rats (Carworth Farms) received feed without HCN, or feed gassed with HCN to the desired concentrations, every 2 days, over a period of 2 years. Chemical analysis confirmed the initial HCN concentration in the feed to be 100 and 300 mg/kg; the feed concentrations dropped to about 50 mg/kg and about 80 mg/kg during the two days between the feed changes respectively	deaths; body weight; feed consumption; haematology (not specified) Biochemical: terminal cyanide and thiocyanate concentrations in blood Organ weights: terminal weights (relative to body weight) of liver, kidneys, heart, brain, spleen, adrenals and testes or ovaries Gross pathology Histopathology of heart, lung, liver, spleen, kidney, adrenal, thyroid, testes or uterus and ovary, cerebrum, and cerebellum	no treatment related effects	NOAEL >80 mg/kg feed equal to 1.5 mg/male rat/day and 1.4 mg/ female rat/day which is equal to about 3.75 and 3.5 mg/kg bw/day respectively (estimated by reviewer)

The study yields an oral NOAEL of more than 3.5 mg/kg bw/day, for the indicated set of endpoints.

No studies specifically aimed at the observation of possible carcinogenic effects of HCN, KCN, or NaCN, have been located by the committee. The available long-term study and 'long' short-term studies have not revealed carcinogenic properties (e.g. Phi79, and How55). However, their experimental setup precludes a definitive conclusion about the carcinogenicity of the investigated cyanides in experimental animals.

6.3.5 *Genotoxicity and cell transformation (based on Bal87b, ATS97, EPA92, and NTP94)*

Salmonella/microsome tests have been carried out with the usual *Salmonella* strains (TA1535, TA1538, TA1537, TA98, TA100, TA97, TA102). Positive effects were only obtained in one study, when HCN was tested with strain TA100 in the absence of metabolic activation, while the other strains employed in this study yielded negative results. KCN was found negative in two studies, when tested with strain TA100 and other strains.

Negative results were obtained in a DNA-repair test with the *Escherichia coli* strains WP67, CM871 and WP2, and a rec assay with the *Bacillus subtilis* strain M45.

NaCN did not induce DNA-strand breaks in cultured mouse lymphoma cells.

KCN did not induce testicular DNA synthesis in mice.

Altogether, these data suggests the absence of genotoxic properties for the three cyanides. The lack of *in vitro* and *in vivo* cytogenetic studies, as well as *in vitro* studies for point mutations, precludes a more definitive conclusion to be drawn.

No cell-transformation studies with one of the three cyanides have been located.

6.3.6 *Reproduction toxicity*

Ballantyne (Bal87b) refers to a study in which the development of the nervous system was inhibited by cyanide in explanted chick embryos (no further details provided).

Doherty *et al*. (Doh82) exposed pregnant golden Syrian hamsters (5-7 per dose group) to NaCN by subcutaneous implantation of osmotic minipumps at the back of the necks. The pumps were implanted on day 6 of gestation; they delivered doses of 0, 0.126, 0.1275, and 0.1295 mmol/kg bw/h (total dose amounted to 30-40 times the subcutaneous LD_{50}); exposure was ended on day 9 of gestation. The hamsters were killed on day 10. The exposure resulted in severe embryotoxic and teratogenic effects (neural-tube effects (exencephaly, encephalocoele, nonclosure), microphthalmia, hydropericardium, crooked tail, reduced crown-rump length, increased percentage of

resorptions), which were accompanied by mild maternal toxicity (weight loss (up to 16%), hypothermia, salivation, ataxia and dyspnea). The teratogenic effects could be suppressed by the administration of thiosulphate.

Olusi *et al*. (Olu79) fed groups of 10 female rats with a diet containing 0, 5 or 10 g KCN/kg feed. None of the cyanide-treated rats became pregnant, whereas 9 out of 10 control rats did become pregnant.

Tewe and Maner (Tew81a) investigated the effect of 1250 mg KCN per kg feed on the reproductive performance of female rats. KCN was added to a low-CN^- cassave diet containing already 21 mg HCN per kg, while the control diet contained 12 mg CN^- per kg. Three treatment periods were discerned: gestation, when the dams were or were not treated; lactation, when the dams were or were not treated; and post weaning, when the new borns were or were not treated. Four groups of dams were composed, depending on their respective treatments during gestation and lactation: control-control, control-treated, treated-control and treated-treated.

The four groups did not significantly differ as regards the following endpoints: body weight gain during gestation and lactation, pups per litter at birth, mortality of pups at birth, body weight of pups at birth, weight gain of pups during lactation, liver and kidney weights of the dams.

The pups were divided into 8 groups after weaning, depending on the dams from which they originated and the treatment regimen to which the pups were subjected after weaning for 28 days (gestation-lactation-postweaning: control-control-control, control-control-treated, etc.).

The treatment of the pups post weaning resulted in significant reductions of growth rate and feed consumption, while no effect of the treatment of the dams was seen for these endpoints. Also the protein efficiency ratio was reduced in the treated pups, and this difference was affected by the treatment of the dams. No effects on liver and kidney weights were seen in the pups. So, the study did not point to an effect on reproductive performance of the dams due to treatment. However, the growth of the pups was affected when they were treated. The effect on protein efficiency ratio suggests a carry-over effect.

In another study, Tewe and Maner (Tew81b) fed groups of 6 pregnant pigs diets containing 30, 277 or 521 mg CN^- per kg feed (KCN was added to the latter two diets; the pigs were treated from one day after breeding till parturition). This treatment had no significant effects on the reproductive performance in terms of litter size, litter size at weaning, birth weight of piglets, daily feed intake of sows and piglets, and body weight gain during gestation. Histopathology of the sows indicated an increase of hyperplasia of kidney glomerular cells due to treatment. Furthermore effects in the thyroid were observed. The foetuses of the high- dose group showed reduced relative weights of

heart and spleen, while a reduced relative thyroid weight was found in the foetuses of the medium-dose group.

The results of these studies can be summarised as follows: 1) NaCN was a clear-cut embryotoxic and teratogenic agent when brought directly into the blood stream of Syrian golden hamsters in such quantities as to cause mild acute toxicity; 2) Very high concentrations of KCN in the feed of female rats (50 and 100 g/kg feed), prevented these animals from becoming pregnant; 3) Concentrations of up to 1251 mg/kg KCN in the feed of pregnant rats did not affect the reproductive capacity of these animals, although the treatment of pigs led to reduced weights of heart, spleen and thyroid in the piglets (which were only treated via the sow in utero).

In addition to these studies, the NTP94 study can be mentioned (see Table 6.12, Annex D), which reveals adverse effects on the male reproductive organs.

Based on the available data, it can be concluded that at overt toxic levels cyanide is an embryotoxic and teratogenic agent; it remains to be determined whether these effects also occur at dose levels which do not cause overt acute toxicity. At much lower dose levels, cyanide does not affect the reproductive performance of rats and pigs, although the experimental setup of the studies in question do not allow a full judgement of possible teratogenic properties.

No studies have been located in which, both males and females were exposed before mating.

6.3.7 In vitro toxicity

Many studies were concerned with the effects of HCN, NaCN or KCN in isolated organs, tissues or in tissue-culture cells. As these studies do not directly support the establishment of an HBR-OEL, but are primarily aimed at the elucidation of effects and mechanisms underlying them, they are not reviewed in the present report.

6.4 Summary

Acute toxicity in humans

- Ample information is available about the oral and respiratory acute toxicity of KCN, HCN and NaCN in humans.
- The following clinical symptoms of acute toxicity are reported: anxiety and excitement, rapid breathing, faintness, weakness, headache (pulsating), constricting sensations in the chest, facial flushing, dyspnoea, nausea, vomiting, diarrhoea, dizziness, drowsiness, confusion, convulsions, incontinence of urine and faeces, coma, respiratory irregularities (listed in Bal87b).

- In case of massive, lethal doses, convulsions are immediately seen, followed by coma and death. When longer exposure to lower doses results in death, the symptoms described above develop in an orderly fashion.
- A characteristic early feature of acute cyanide poisoning is tachypnoea and hyperpnoea, resulting in an increased tidal volume.
- Respiratory exposure for several hours to 20 mg/m^3 HCN leads to slight acute effects, while exposure to concentrations higher than 120 mg/m^3 can already be fatal. Thus, it can be concluded that the acute respiratory toxicity of HCN shows a steep dose dependence.
- One case study shows that immersion of the hand in HCN leads to effects within 5 minutes.
- The survival of serious acute cyanide poisoning may lead to severe neurotoxicological sequelae (parkinsonism and morphological damage in the brain).

Short-term and long-term toxicity in humans

- Some case studies suggest that human cyanide toxicity is not restricted to acute effects and their sequelae, but that effects may gradually develop upon repeated exposure, in particular neurotoxicity and goitre. However, due to the lack of exposure data, it is not possible to relate these effects to exposure in a quantitative way.
- An epidemiological study (ElG75) in which electroplating workers were compared with workers supposedly not exposed to cyanides, showed a much higher prevalence in the first group of symptoms associated with acute cyanide poisoning. In addition, enlarged thyroids were found in most of the exposed workers, pointing to goitre. Furthermore, this group had higher haemoglobin levels, lymphocyte counts and had cyanhaemoglobin in their blood.
  A high correlation was obtained for the thiocyanate concentrations in urine and mean air cyanide concentrations, the first being equal to 0.65 times the second. Cyanide air-concentrations of 4.2-12.4 ppm (4.7-13.9 mg/m^3) were observed. Although the causal relationship between cyanide exposure and the symptoms is not proved by the study, it is deemed highly probable by the committee.
- Notwithstanding its methodological weaknesses, the study of Blanc *et al*. (Bla85) clearly suggests a relationship between cyanide exposure and severity of cyanide-associated symptoms. Furthermore, this study shows a persistency of acute effects over a period of more than seven months. However, no quantitative relationship between exposure and severity of effects could be established.

- The studies of Hlynczak *et al*. (Hly80a and Hly80b) suggest effects of respiratory exposure to concentrations of up to 7.5 mg/m^3 on the serum levels of zinc, calcium and iron and the activity of the serum enzyme LDH.

Irritation and sensitisation in experimental animals

- No studies on the skin- and eye-irritating properties, as well as the sensitising properties of HCN, NaCN and KCN in experimental animals have been located.
- Breath-rate and breath-pattern analysis indicates that inhalation of HCN by mice causes respiratory irritation.
- Skin contact with HCN or solutions of its salts leads to skin irritation in humans. No data on eye irritation and skin sensitisation in humans have been located.

Acute lethality in experimental animals

- The lethality of exposure to HCN, NaCN or KCN has been extensively investigated in several animal species, after oral, dermal, respiratory, ocular, intravenous, subcutaneous, intraperitoneal and intramuscular exposure. The ranges of the LD_{50} and LC_{50} values which are presented in this report, are listed in Table 6.14.

Table 6.14 Ranges of LD_{50} and LC_{50} values of the three cyanides.

route	value	mmol/kg bw or ppm
oral	LD_{50}	0.09-0.15
dermal (dissolved in water)	LD_{50}	0.26-0.34
respiratory (30 min)	LC_{50}	134-410
ocular	LD_{50}	0.04-0.12
intravenous	LD_{50}	0.02-0.03
intramuscular	LD_{50}	0.02-0.06
intraperitoneal	LD_{50}	0.06-0.12

This table clearly demonstrates the well-known high acute lethality of exposure to HCN, NaCN or KCN.

- In case of respiratory exposure, Habers rule is not fulfilled, as the LC_{50} increased more strongly than expected on the basis of a constant product of concentration and exposure time.
- Dermal exposure to powders of the salts leads to substantial lethality when the skin is abraded or wetted, in which cases the LD_{50} values do not differ much from those obtained for exposure of the intact skin to aqueous solutions.

Other acute effects in experimental animals

- Acute exposure to (near) lethal levels leads to the following overt clinical effects: dyspnea, irregular, shallow and gasping breathing, ataxia, tremors, retrocolic spasms, tonic spasms, loss of consciousness, convulsions, and asphyxiation.
- Much qualitative and mechanistic information is available on the various sublethal effects of single high doses (approaching lethal levels). This information does not allow for the establishment of dose-response (effect) relationships. In short the following categories of effects can be mentioned:
  - Changes in brain neurochemistry, affecting concentrations of neurotransmittors and related compounds, calcium and GMP.
  - Lipid peroxidation and compromised antioxidant defence in the brain.
  - Stimulation of the sympathoadrenal system.
  - Electrophysiological effects in the brain.
  - Histological lesions in the brain.
  - Impairment of motor performance and, possibly, cognitive functions.
  - Changed perfusion of the brain.
  - Various cardiovascular effects.
  - Effects on peripheral receptors and parts of the brain which regulate respiration.
  - Clear-cut effects on parameters of energy metabolism.

Short-term toxicity in experimental animals

- Repeated respiratory exposure of dogs to acutely toxic doses (50 mg/m^3) leads to severe histological lesions in the brain. No histological effects were observed in heart, lungs, and adjacent arteries of rabbits after a four-weeks long respiratory exposure to 0.5 mg/$m^{3.}$
- After short-term oral exposure various effects have been observed in experimental animals, among them: effects on the thyroid, central nervous system, behaviour, glucose metabolism, selenium metabolism, glutathione-peroxidase activity, ATP-ase activity and male reproductive organs. No overall oral NOAEL could be established for short-term toxicity, as effects on behaviour, central nervous system and male reproductive organs were already observed at the lowest applied doses of 0.4, 0.5, and 3 mg/kg bw/day respectively.

Long-term toxicity and carcinogenicity in experimental animals

- No effects were seen in an oral study with rats which lasted for 2 years in which a rather extensive range of endpoints were investigated. The highest dose applied was about 3.5 mg/kg bw/day.
- The long-term study as well as the ‘longer’ short-term studies did not reveal clear signs of carcinogenicity. However, their experimental set up precludes a definitive

conclusion about the carcinogenicity of the investigated cyanides in experimental animals.

Genotoxicity

- The available genotoxicity studies suggest that the three cyanides are devoid of genotoxic properties. However, studies deemed essential by the committee are lacking, i.e., studies on the *in vitro* and *in vivo* induction of cytogenetic effects and point-mutation studies with mammalian tissue-culture cells.

Teratogenicity and reproduction toxicity in experimental animals

- NaCN has been shown to possess embryotoxic and teratogenic properties when brought directly into the blood stream of Syrian golden hamsters in such quantities as to cause mild acute toxicity.
- Very high concentrations of KCN in the feed of female rats prevented these animals from becoming pregnant.
- Concentrations of up to 1271 mg/kg KCN in the feed of pregnant rats and pigs did not affect the reproductive capacity of these animals.
- Concentrations of up to 1271 mg/kg KCN in the feed of pregnant pigs resulted in reduced weights of heart, spleen, and thyroid in the piglets exposed in utero via the sow.
- Based on the available data, the authors conclude that cyanides are embryotoxic and teratogenic at maternally toxic doses. No data are available on the embryotoxicity and teratogenicity at lower, not maternally toxic dose levels.
- No adequate reproduction-toxicity studies are available.

Chapter 7

Existing guidelines, standards and evaluations

7.1 General population

Chronic daily oral reference doses (RfD) of 0.02 mg/kg/day for hydrogen cyanide, of 0.05 mg/kg/day for potassium cyanide, and of 0.04 mg/kg/day for sodium cyanide have been established by the EPA. These RfDs are based on the NOAEL of 11.2 mg/kg/day for systemic effects in rats fed hydrogen cyanide for two years (see Section 6.2.4 in this report). Cyanide (CN and CN-compounds) has been classified D for carcinogenicity by EPA, indicating that cyanide is not classifiable as to human carcinogenicity (ATS97).

7.2 Working population

7.2.1 Occupational exposure limits

Occupational exposure limits for hydrogen cyanide, and total cyanide in the Netherlands and some other countries are presented in Table 7.1.

The NIOSH (ACG02) based their 5 mg/m^3 (4.7 ppm) 10-minute ceiling limit largely on the report of El Ghawabi *et al*. (ElG75; see Section 6.1.3 in the present report).

A ceiling of 5 mg cyanide/m^3, with a skin notation, is recommended by the ACGIH (ACG02) for alkali cyanides and calcium cyanide in order to prevent irritation and injury to the respiratory passages, as well as the chronic effects of cyanide, and to provide a margin of safety against acute effects.

The Deutsche Forschungsgemeinschaft (DFG) (DFG01) reviewed hydrogen cyanide and total cyanides in 2000/2001 and reduced the MAK to 2.1 mg/m^3 (1.9 ppm) for hydrogen cyanide and 2 mg/m^3 for total cyanides.

7.2.2 Biological limit values

There are no biological limit values available for hydrogen cyanide, sodium cyanide and potassium cyanide (see also section 5.5).

Table 7.1 Occupational exposure standards in various countries.

country organisation	occupational exposure limit		time-weighted average	type of exposure limit	note[a]	lit ref[b]	year of adoption[c]
	mg/m^3	ppm					
hydrogen cyanide							
The Netherlands							
-ministry	11	10	ceiling	administrative force	S	SZW02	unknown
Germany							
-DFG	2.1	1.9	8 h	MAK	S	DFG01	unknown
Great Britain							
-HSE	11	10	15 min	MEL	S	HSE02	unknown
Denmark	5	5	8 h		S	Arb96	unknown
USA							
-ACGIH	5[d]	4.7[d]	ceiling	TLV ceiling	S	ACG02	1994
-OSHA	11	10	8 h	PEL final rule limit	S	OSH93	1993
-NIOSH	5	4.7	15 min	REL	S	ACG02	unknown
total cyanides (CN)							
The Netherlands							
-ministry	5		8 h	administrative force	S	SZW02	unknown
Germany							
-DFG	2		8 h	MAK	S	DFG01	unknown
Great Britain							
-HSE	5		8 h	OEL	S	HSE02	unknown
Sweden	5		ceiling	occup. exp. lim. val.	S	SNB93	unknown
Denmark	5[d]		ceiling	lim. val. air cont.	S	Arb96	unknown
USA							
-ACGIH	5[e]		ceiling	TLV ceiling	S	ACG02	1994
-OSHA	5		8 h	PEL final rule limit		OSH02	1993
-NIOSH	5		10 min.	REL		ACG92	1976

[a] S=skin notation; which means that skin absorption may contribute considerably to body burden. Sens=substance can cause sensitisation

[b] reference to the most recent official publication of occupational exposure limits

[c] year that this limit was officially adopted or established

[d] as CN

[e] as CN from hydrogen cyanide, calcium cyanide, potassium cyanide, or sodium cyanide

Chapter 8

Hazard assessment

8.1 Groups at extra risk

At extra risk are people with hereditary disorders associated with a hampered cyanide detoxification (Leber's hereditary optic atrophy, dominantly inherited optic atrophy and recessively inherited optic atrophy) (DEC95; Wil87). These people may accumulate cyanide to toxic levels, whereas a similar exposure is devoid of any adverse effects in people not affected by these disorders.

8.2 Assessment of health hazard

Cyanide most commonly occurs as hydrogen cyanide and its salts - sodium and potassium cyanide. Cyanides are both man-made and naturally occurring substances. Cyanides are released to the environment mainly from industrial sources. Its properties are well investigated.

Toxicity due to acute exposure

The human information on acute cyanide toxicity is hampered by the fact that it is based largely on case studies, which implies that uncertainty about actual dose levels and exposure routes prevails. Furthermore, a restricted number of non-invasive toxicological endpoints is investigated in most studies. However, the human data provided by Hall (Hal87) and the US EPA (EPA92) suggest a dose range of 20 to 40

mg/m^3 HCN (18 to 36 ppm) with only slight acute effects after several hours of exposure. No case studies have been located in which acute effects were found at lower levels. Furthermore, the studies give a rather steep dose-response relationship for acute effects: while concentration of 20-40 mg/m^3 lead to only slight symptoms, concentrations larger than 135 mg/m^3 (120 ppm) are fatal. Death is preceded by coma and caused by respiratory failure or cardiac arrest, which are the direct result of inhibition of cytochrome C oxidase by cyanide.

Most animal studies are either solely focused on lethality, or on the detection of pre- or sublethal effects and the elucidation of the mechanisms underlying these effects. Information on the dose-dependence of these effects is virtually absent.

In addition to acute systemic effects, the three cyanides have skin irritating properties. HCN also causes irritation of the respiratory tract. No information is available on the sensitising properties of the three cyanides, in experimental animals nor in humans. However, sensitisation has never been recognised as a problem from the extensive casuistry on cyanide exposure.

Based on these data the committee considers the acute human data as the most sensitive for cyanide. The steepness of the dose-response relationship and the severity of the acute effects in humans imply at the same time that utmost care should be taken to prevent this exposure level from being exceeded, not even for a short time. Therefore, the commission proposes to assess a ceiling value for the acute health effects of HCN.

Starting from the lowest effect dose of 20 mg/m^3 (LOAEL) and in view of the steep overall dose-response relationship and the severe acute cyanide toxicity in humans (Hal87 and EPA92), the committee considers an assessment factor of 2 sufficient for the extrapolation from LOAEL to NAEL which results in a ceiling value of 10 mg/m^3 (9 ppm) for HCN.

The difference in acute systemic toxicity between the three cyanides is solely dependent by their availability for absorption and their absorption rate. Once absorbed, they induce the similar types of effects, depending on the location of absorption and amount of CN^- absorbed per unit of time. The available data do not indicate differences in respiratory toxicity between HCN, KCN, and NaCN, if compared on the basis of the absorbed amount of CN^-. Thus, equal ceiling values can be established for the three compounds, if they are expressed as CN^- concentrations in the air. The ceiling value of 10 mg/m^3 derived for HCN corresponds with 10 mg CN^- per m^3, and this value, in its turn, corresponds with 18 mg NaCN per m^3 and 24 mg KCN per m^3 (both as inhalable dust). The latter two values, then, represent the ceiling values for acute health effects for the two salts. As the three compounds are fully comparable as regards their toxicological endpoints and effects, they should not be regulated independently.

Therefore, the committee establishes a ceiling value of 10 mg/m^3 as CN^- from any combination of the three compounds for acute exposure.

Toxicity due to longer-term exposure including reproduction toxicity and carcinogenicity

There is no evidence in humans for carcinogenicity or effects on reproduction. The epidemiological study of El Ghawabi *et al*. (ElG75) on chronic exposure of workers to cyanide in electroplating industries, is considered valid for deriving a HBR-OEL for longer-term exposure by the committee. This study, with breathing zone air concentrations ranging from 4.2 to 12.4 ppm (4.7-13.9 mg/m^3), links a series of cyanide-exposure-related effects to chronic cyanide exposure. Although no dose dependence could be established, the nature of the effects clearly points to a causal relationship with cyanide exposure. In particular the clear signs of goitrogenicity can be regarded as cyanide (i.e., thiocyanate) specific and are taken as the most sensitive effect by the committee. The interpretation of the study is hampered by the uncertainty about dermal and oral exposure and about the exposure levels in the past. The risk may be overestimated when dermal or oral exposure substantially contributed to the total exposure or when exposure levels in the past were substantially higher than those measured during the study. This is however regarded as a reasonable worst case for establishment of a HBR-OEL for longer- term exposure. Moreover, the two studies of Hlyñczak *et al*. (Hly80a and Hly80b) suggest that biochemical effects (increases of concentrations of metals and enzyme activities in serum) occur at comparable respiratory exposure levels (less than 7.5 mg/m^3 (6.7 ppm)).

In animals there is no evidence for the carcinogenicity of cyanide. However, the experimental setup of the studies precludes a definitive conclusion about the carcinogenicity of the investigated cyanides. Cyanides are embryotoxic and teratogenic at maternally toxic doses. The reproduction toxicity has not adequately been investigated.

A number of studies were concerned with the effects of longer-term exposure in experimental animals. In most of these studies one or few relatively high doses were investigated, as they were aimed more at the detection and elucidation of the effects than at the establishment of NOAELs. Furthermore, most studies had a rather limited scope as regards the number of endpoints investigated. According to the committee the animal studies can not serve as a basis for an OEL for effects of longer-term exposure.

The committee takes as starting point the lowest- observed-adverse-effect -level (LOAEL) of 4.2 ppm (4.7 mg/m^3) for deriving a HBR-OEL. Due to the effects observed in the exposed population at 4.2 ppm and the absence of a dose-response relationship in the study, the commission recommends using a factor 5 for the

extrapolation from LOAEL to NAEL. By applying this assessment factor, the committee recommends a HBR-OEL for longer-term toxicity of 1 mg/m^3 (0.9 ppm). This HBR-OEL for HCN represents a time-weighted average over a working day of 8 h. The respective HBR-OELs for NaCN and KCN can be calculated as 1.8 and 2.4 mg/m^3, 8 h TWA, as inhalable dust.

Skin notation

The study of Dugard (Dug87) yielded very high skin permeability constants for CN^- (3.5×10^{-4} cm/h) and HCN (10^{-2} cm/h), when present in aqueous solutions. If, for instance, the skin is exposed to a solution containing 100 mg/ml non-ionized HCN for 1 h, a total amount of about 2 g is absorbed. This amount has to be compared with 0.1 g absorbed after respiratory exposure to 10 mg/m^3 during 8 h, assuming a respiratory volume of 10 m^3. Therefore, the committee recommends that skin notations should be applied for all three cyanides.

8.3 Health-based recommended occupational exposure limits

The committee establishes a ceiling value of 10 mg/m^3 (9 ppm) for HCN, a ceiling of 18 mg/m^3 for NaCN, and a ceiling of 24 mg/m^3 for KCN (for NaCN and KCN as inhalable dust). As the three compounds are fully comparable as regards their toxicological endpoints and effects, they should not be regulated independently. Therefore, the committee establishes a ceiling value of 10 mg/m^3 as CN^- from any combination of the three compounds for acute exposure.

The committee establishes an HBR-OEL, 8 h TWA of 1 mg/m^3 (0.9 ppm) for HCN, an HBR-OEL, 8 h TWA of 1.8 mg/m^3 for KCN and an HBR-OEL, 8 h TWA of 2.4 mg/m^3 for NaCN (for NaCN and KCN as inhalable dust). As the three compounds are fully comparable as regards their toxicological endpoints and effects, they should not be regulated independently. Therefore, the committee establishes an HBR-OEL, 8 h TWA of 1 mg/m^3 as CN^- from any combination of the three compounds.

A skin notation should be attached to all three compounds.

Chapter 9

Recommendations for further research

In view of the fact that the three cyanides can be regarded as the archetypical poisons, it is surprising that their toxicological dossiers are characterised by a number of obvious shortcomings, which hamper an adequate evaluation of the occupational health risks and the establishment of a well founded HBR-OEL.

In general, it can be stated that the dossiers give a fairly complete qualitative impression of cyanide toxicology. A broad range of adverse effects have been identified, while mode of action and toxicokinetics have been thorougly investigated. The shortcomings are in particular concerned with the quantitative aspects of the toxicity. Information of the relationship between, on one hand, nature and intensity of exposure and, on the other, severity of effects is only scanty.

The shortcomings can to a large extent be met by the following studies:

- Acute and short-term respiratory studies with various species, which allow the establishment of dose-effect/response relationships. Apart from toxicological endpoints usually investigated in such studies, the sensitive endpoints already identified at high doses should be investigated in these studies. In particular the following should receive attention:
  - neurochemistry,
  - histopathology of the central nervous system and the heart,
  - behaviour,
  - endpoints associated with cardio-vascular functions,
  - electrophysiology, and
  - endpoints associated with energy metabolism.

These endpoints should be followed over fairly long recovery periods.

- The clear-cut teratogenicity observed when NaCN is brought directly into the blood stream, indicates the necessity of respiratory studies in which this effect is studied in a regular manner.

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A Request for advice

B The committee

C Comments on the public draft

D Results of short-term toxicity studies with the three cyanides Table 6.12

E Abbreviations

F DECOS-documents

Annexes

Annex **A**

Request for advice

In a letter dated October 11, 1993, ref DGA/G/TOS/93/07732A, to, the State Secretary of Welfare, Health and Cultural Affairs, the Minister of Social Affairs and Employment wrote:

Some time ago a policy proposal has been formulated, as part of the simplification of the governmental advisory structure, to improve the integration of the development of recommendations for health based occupation standards and the development of comparable standards for the general population. A consequence of this policy proposal is the initiative to transfer the activities of the Dutch Expert Committee on Occupational Standards (DECOS) to the Health Council. DECOS has been established by ministerial decree of 2 June 1976. Its primary task is to recommend health based occupational exposure limits as the first step in the process of establishing Maximal Accepted Concentrations (MAC-values) for substances at the work place.

In an addendum, the Minister detailed his request to the Health Council as follows:

The Health Council should advice the Minister of Social Affairs and Employment on the hygienic aspects of his policy to protect workers against exposure to chemicals. Primarily, the Council should report on health based recommended exposure limits as a basis for (regulatory) exposure limits for air quality at the work place. This implies:

- A scientific evaluation of all relevant data on the health effects of exposure to substances using a criteria-document that will be made available to the Health Council as part of a specific request for advice. If possible this evaluation should lead to a health based recommended exposure limit, or, in

the case of genotoxic carcinogens, a ‘exposure versus tumour incidence range’ and a calculated concentration in air corresponding with reference tumour incidences of 10^{-4} and 10^{-6} per year.

- The evaluation of documents review the basis of occupational exposure limits that have been recently established in other countries.
- Recommending classifications for substances as part of the occupational hygiene policy of the government. In any case this regards the list of carcinogenic substances, for which the classification criteria of the Directive of the European Communities of 27 June 1967 (67/548/EEG) are used.
- Reporting on other subjects that will be specified at a later date.

In his letter of 14 December 1993, ref U 6102/WP/MK/459, to the Minister of Social Affairs and Employment the President of the Health Council agreed to establish DECOS as a Committee of the Health Council. The membership of the Committee is given in annex B.

Annex **B**

The committee

- GJ Mulder, *chairman*
  professor of toxicology; Leiden University, Leiden
- RB Beems
  toxicologic pathologist; National Institute of Public Health and the Environment, Bilthoven
- PJ Boogaard
  toxicologist; Shell International Petroleum Company, The Hague
- PJ Borm
  toxicologist; Heinrich Heine Universität Düsseldorf (Germany)
- JJAM Brokamp, *advisor*
  Social and Economic Council, The Hague
- DJJ Heederik
  epidemiologist; IRAS, Utrecht University, Utrecht
- LCMP Hontelez, *advisor*
  Ministry of Social Affairs and Employment, The Hague
- TM Pal
  occupational physician; Netherlands Center for Occupational Diseases, Amsterdam
- IM Rietjens
  professor of toxicology; Wageningen University, Wageningen.
- H Roelfzema, *advisor*
  Ministry of Health, Welfare and Sport, The Hague

- T Smid
  occupational hygienist; KLM Health Safety & Environment, Schiphol and professor of working conditions, Free University, Amsterdam
- GMH Swaen
  epidemiologist; Maastricht University, Maastricht
- RA Woutersen
  toxicologic pathologist; TNO Nutrition and Food Research, Zeist
- P Wulp
  occupational physician; Labour Inspectorate, Groningen
- ASAM van der Burght, *scientific secretary*
  Health Council of the Netherlands, The Hague
- JM Rijnkels, *scientific secretary,*
- Health Council of the Netherlands, The Hague

The first draft of the present advisory report was prepared by Dr WK de Raat and CMMG Vervoort, from TNO Voeding, Zeist, by contract with the Ministry of Social Affairs and Employment.

Secretarial assistance: A Aksel
Layout: J van Kan

Annex **C**

The comments on the public review draft

A draft of the present report was released in November 1999 for public review. The following organisations and persons have commented on the draft document:

- A Aalto, Ministry of Social Affairs and Health, Occupational Safety and Health Division, Tampere, Finland;
- WF ten Berge, CSEH&T, DSM , Heerlen, The Netherlands;
- P. van der Hoeven, CEFIC Cyanides Sector Group, Bruxelles, Belgium;
- P. Rocchi, SAS-VGW Arbodienst Shell Perniss, Hoogvliet, The Netherlands.

Annex **D**

Results of short-term toxicity studies with the three cyanides Table 6.12

spec.	route	comp.	doses	exposure regimen	investigated endpoints	effects	experimental limit value (non-acute effects)	ref.
Dog	Respiratory	HCN	50 mg/m^3 (44.5 ppm)	Group of 4 dogs; 12 exposures of 30 min; 1 exposure per 8 days. No controls Group of 4 dogs; 14 or 19 exposures of 30 min; 1 exposure per 2 days. No controls	Deaths, general clinical observations; neurological and behavioral observations; gross pathology and histopathology of the brain	Deaths: 3/12 Effects during exposure: dyspnoea, vomiting, diarrhoea, muscular tremors, affected locomotion (waggeling gait, stiff limbs, rapid turning), affected equilibrium, general convulsions, tonic contraction of limbs. Brain pathology, vascular lesions, cellular lesions, particularly in cerebellum and medulla oblongata; glial reaction throughout whole central nerveus system	LOAEL 50 mg/m^3 (44.5 ppm)	Val52
Rabbit	Respiratory	HCN	0 and 0.5 ppm (0.56 mg/m^3)	Groups of 18-24 rabbits were continuously exposed for 1 or 4 weeks	Histopathology of coronary arteries, aortic arch, descending thoracic aorta, pulmonary artery and lung	No treatment-related effects	NOAEL > 0.5 ppm (> 0.56 mg/m^3)	Hug79
Rabbit	Respiratory	HCN	0 and 0.5 ppm (0.56 mg/m^3)	Rabbits were continuously exposed for 4 weeks	Ultrastructure of myocard	No treatment-related effects	NOAEL > 0.5 ppm (> 0.56 mg/m^3)	Summar-ized in EPA92

spec.	route	comp.	doses	exposure regimen	investigated endpoints	effects	experimental limit value (non-acute effects)	ref.
Pigs	Oral	KCN	0, 0.4, 0.7 and 1.2 mg/kg bw/day	Groups of 3 juvenile (5 weeks) pigs, containing at least 1 male (castrated) and l female (unspayed), were treated daily for a period of 24 weeks with KCN dissolved in water	Biochemical: T_3, Triiodothyromine, T_4 thyroxin, fasting blood glucose, thiocyanate and cyanide in blood Behavior; social, antagonistic, exploratory, ingestive, excretory, operant conditioning, limping, stiffness, diarrhoea, vomiting, convulsions, shivering	Biochemical: decrease of T_3 and T_4 in all treated groups; increase of fasting bloodglucose levels in all treated groups; correlation between thiocyanate in blood and CN intake (r=0.83) Behaviour: decrease in dominance behavior; variable effect on vocalizing; decrease in fighting; decreased aggression; increase in victimization; decrease in exploratory behaviour, less aggressive feeding pattern; increased distractibility from eating; decreased pica; increased anaesthesia recover) time; increased limping and stiffness; increased vomiting; increased convulsions and shivering	LOAEL 0.4 mg/kg bw/day based on both biochemical and behavioral endpoints	Jac88
Rat	Oral	KCN	0 and 375 mg/l drinking water	Groups of 4 adult male rats were giving drinking water with or without KCN for 2 weeks; each rat was then injected with radioactive selenite, whereupon urine and faeces were collected for 15 days	Urinary selenium excretion; selenium in tissues	Increased urinary selenium excretion; shorter half-life of selenium in the body	LOAEL 375 mg/1 drinking water	Bei84
Rat	Oral	KCN	0 and 375 mg/l drinking water	Groups of 5 adult male rats (Sprague Dawley) were giving drinking water with or without KCN for 3, 6 and 9 weeks.	Glutathione peroxidase activity in liver, kidneys, blood, muscle, and testes	Reduced glutathione peroxidase activity in liver, kidney, muscle, and blood	LOAEL 375 mg/l drinking water	Bei84
Rat	Oral	KCN	0 and 1.5 g/kg feed	Groups of 10 male weanling rats received feed restricted in iodine, Vitamin B_{12} and DL-methionine or feed without these restrictions; each feed was fed with and without 1.5 g/kg feed of KCN, which brings the total number of groups at 4. The treatment period lasted 10.5 months.	Body weights; plasma thyroxine; thyroxine secretion rate Histopathology of brain, optic and sciatic nerves, spinal cords, and thyroids	Body weights: markedly reduced Biochemical: decrease of thyroid function demonstrated by decreased plasma thyroxine concentrations and thyroxine secretion Histopathology: "Modest primary myelin degeneration in spinal cord white matter ..." in rats with restricted diet, increase of these lesions when fed KCN	LOAEL 1.5 g/kg feed (75 mg/kg bw/day according to EPA92)	Phi89
Rat	Oral	KCN	0 and 1.87 g/kg feed	Eight groups of 8 rats were fed four different types of feed differing in iodine and protein content. Treatment lasted 56 days.	Clinical: body weight, feed intake, feed efficiency organ weights: liver and kidneys Biochemical: thiocyanate and iodine in blood and urine, serum protein, rhodanese activity in liver and kidney	Clear increases of blood and urine thiocyanate levels	NOAEL > 1.87 g/kg feed > 100 mg/kg bw/day (estimated by reviewer)	Tew82

spec.	route	comp.	doses	exposure regimen	investigated endpoints	effects	experimental limit value (non-acute effects)	ref.
Rabbit	Oral	KCN	0 and 1.6 g/kg feed	Groups of 6 male rabbits were treated for a period of 6 weeks	Activity of Na^+-K^+-ATPase, Ca^{2+}-ATPase and Mg^{2+}-ATPase in various tissues	Marked and significant decreases in activity for ileum, colon, liver, and kidney	LOAEL 1.6 g/kg feed 91 mg/kg bw/day (estimation of reviewer)	Oko94
Rat	Oral	KCN	0, 50 and 100 g/kg feed	Groups of 10 adult female rats were fed for 14 weeks with feed containing the indicated KCN concentrations	Body weight gain Haematology: haemoglobin, packed cell volume Organ weights: thyroid and spleen Biochemical: serum protein, serum thyroxine Histopathology: organs investigated not indicated	Marked decreases of body weight, haemoglobin, packed cell volume, total serum protein, serum thyroxine, relative spleen weight; increase of relative thyroid weight Centrilobular liver cell necrosis Caecum and colon benign tumours: 5 out of 10 rats in 50 g/kg group and 7 out of 10 rats in 100 g/kg group; tumours contained hypertrophic muscle fibres	LOAEL 50 g/kg feed	Olu79
Rats and mice	Oral	NaCN	0, 3, 10, 30, 100 and 300 mg/l drinking water	Groups of 10 F344/N rats per sex and group 10 B6C3F1 mice per sex received drinking with the indicated concentrations of NaCN for 13 weeks. Doses are equal to 0, 0.3, 0.9- 1.0, 2.7-3.2, 7.5-8.2, 23.5-23.6 mg/kg bw/day for rats and 0, 0.5-0.6, 1.8-2.1, 5.1-6.2, 16.2-18.1 and 45.9-54.3 mg/kg bw/day for mice, based on mean consumed amounts of water	Clinical: deaths, general condition, terminal body weight, water consumption Haematological: extensive series of parameters. Biochemical (blood): urea nitrogen, crealinine, total protein, albumin, alanine aminotransferase, alkaline phosphatase, creatinine kinase, sorbitol dehydrogenase, 5'-nucleotidase and total bile acids. Biochemical (urine): thiocyanate, sorbitol dehydrogenase, N-acetyl-β-D-glucoasiminidase, ribonuclease, pH. Reproduction: sperm motility, epididymal spermatozoal data, spermatogenesis, vaginal cytology, estrous-cycle length, percentage of cycles spent in the various stages Cross pathology: all animals. Histopathology: animals of the 0 and 300 mg/l groups: adrenals, brain, clitoral glands, oesophagus, eyes (if grossley abnormal), femur and marrow, gallbladder (mice only), gross lesions and tissue masses, heart, kidneys, large intestine, liver, lungs, lymph nodes, mammary gland, nasal cavity and turbinates, ovaries, pancreas, parathyroid glands, pharynx (if grossly abnormal). pituitary, preputial glands, prostrate, salivary gland, seminal vescicle, skin, small intestine, spinal cord/sciatic nerve, spleen, stomach, testes, thigh muscle, thymus, thyroid, trachea, urinary bladder, uterus, vagina	Rats: Decrease of water consumption in 100 and 300 mg/l groups. Dose dependent significant decrease of cauda epididymal weights in all exposed groups; significant decreases of epididymal and testis weights in the 300 mg/l group; decrease of number of spermatid heads at 300 mg/l; reduced sperm motility in all exposed groups; females of the 100 and 300 mg/l groups spent more time in pro-oestrus and dioestrus and less time in metoestrus and oestrus. Mice: Decrease of water consumption in 100 and 300 mg/l groups. Decreased body-weight gain at 300 mg/l. Decrease of epididymal and cauda epididymal weights at 300 mg/l.	Rat, LOAEL 0.3 mg/kg bw/day Mouse, NOAEL 18.1 mg/kg bw/day	NTP94

spec.	route	comp.	doses	exposure regimen	investigated endpoints	effects	experimental limit value (non-acute effects)	ref.
Dog	Oral	NaCN	0.5 mg/kg bw/day	Three dogs received the indicated dose for 15 months	Histopathology of central nerveus system	Degenerative changes in ganglion cells	LOAEL 0.5 mg/kg bw/day	Summarized in EPA92
Dog	Oral	NaCN	0 and 5.7 mg/kg bw/day	Dogs were treated for 30-32 days	Feed consumption, body-weight gain, haematology. Extensive histopathology	No treatment-related effects	NOAEL > 5.7 mg/kg bw/day	Summarized in EPA92
Rat	Intraperitoneal	NaCN	0, 2.5-4 mg/kg bw/day	Groups of 20 male Wistar rats were treated daily with an intraperitoneal injection of NaCN in water over a period of 5 weeks; the dose increased from 2.5 mg/kg bw on day 1 to 4 mg/kg bw on day 31.	Acute cyanide effects. Clinical effects. Biochemical: liver cytochrome oxidase activity, phospholipid synthesis in liver mitochondria, adenine nucleolide binding on liver mitochondrial membrane, copper content of liver Pathology: gross and microscopical pathology of liver, kidneys and brain.	Acute cyanide effects: respiratory distress, cyanosis, convulsions, loss of consciousness, recovery after 15-30 min, tolerance developed after several days at 2.5 mg.kg bw. Clinical: slower body-weight gain Biochemical: reduced adenine nucleotide binding on liver mitochondrial membranes; reduced copper content of the liver. Pathology: no pathological lesions observed	LOAEL 2.5 mg/kg bw/day	Gal76
Mouse	Subcutaneous	KCN	0 and 12 mg/kg bw/day	Groups of 6 male non-Swiss Albino mice were injected twice a day for 7 days.	Clinical effects. Biochemical: catecholamines and malonaldehydes in brain. Behavior locomotor activity, catalepsy, akinesia. Immunohistochemistry: tyrosine hydroxylase in brain	Clinical: laboured breathing, depression. piloerection, tremors, convulsions, muscular incoordination; these effects lasted for up to 1 hour after injection of KCN. Biochemical: decrease of catecholamines in striatum and hippocampus; increase of malonaldehyde in striatum and hippocampus Behavior 30-35% of animals showed decreased locomotor activity, akinesia, catalepsy, the first two effects dissappear after administration of *l*-DOPA. Immunohistochemistry: reduced number of tyrosine-hydroxylase positive cells in substantia nigra	LOAEL 12 mg/kg bw/day	Kan94

Annex **E**

Abbreviations

bp	boiling point
EC_{50}	concentration at which a described effect is found in 50% of the exposed animals or at which the effect is decreased up to 50% of the control value
HBR-OEL	health based recommended occupational exposure limit
h	hour
IC_{50}	concentration at wAbbreviationshich inhibition of a certain function is found up to 50% of the control value
LC_{50}	lethal concentration for 50% of the exposed animals
LC_{lo}	lowest lethal concentration
LD_{50}	lethal dose for 50% of the exposed animals
LD_{lo}	lowest lethal dose
LOAEL	lowest observed adverse effect level
MAC	maximaal aanvaarde concentratie (maximal accepted concentration)
MAEL	minimal adverse effect level
MAK	Maximale Arbeitsplatz Konzentration
MOAEL	minimal observed adverse effect level
MTD	maximum tolerated dose
NAEL	no adverse effect level
NEL	no effect level
NOAEL	no observed adverse effect level
OEL	occupational exposure limit
PEL	permissible exposure limit
ppb	parts per billion (v/v)10^{-9}
ppm	parts per million (v/v)10^{-6}
RD_{50}	concentration at which a 50% decrease of respiratory rate is observed
REL	recommended exposure limit
STEL	short term exposure limit

tgg	tijd gewogen gemiddelde
TLV	threshold limit value
TWA	time weighted average
V_{max}	maximal reaction velocity of an enzyme

Organisations

ACGIH	American Conference of Governmental Industrial Hygienists
CEC	Commission of the European Communities
DECOS	Dutch Expert Committee on Occupational Standards
DFG	Deutsche Forschungsgemeinschaft
EPA	Environmental Protection Agency (USA)
FDA	Food and Drug Administration (USA)
HSE	Health and Safety Executive (UK)
IARC	International Agency for Research on Cancer (WHO)
INRS	Institut National de Recherche et de Sécurité (France)
NIOSH	National Institute for Occupational Safety and Health (USA)
NTP	National Toxicology Programme (USA)
OECD	Organisation for Economic Cooperation and Development
OSHA	Occupational Safety and Health Administration (USA)
RTECS	Registry of Toxic Effects of Chemical Substances
SER	Social and Economic Council (Sociaal-Economische Raad NL)
WATCH	Working Group on the Assessment of Toxic Chemicals (UK)
WHO	World Health Organisation

Toxicological terms

bid	*bis in diem* (twice per day)
bw	body weight
CARA	chronic non-specific respiratory diseases
CHD	coronary heart disease
CNS	central nervous system
ECG	electrocardiogram
EEG	electro encephalogram
FCA	Freunds Complete Adjuvans
FEV	forced expiratory volume
FSH	follicle stimulating hormone
GD	gestation day(s)
GPMT	guinea pig maximisation test
GSH	glutathione
HLiA	hamster liver activated
IHD	ischaemic heart disease
im	intramuscular
ip	intraperitoneal
ipl	intrapleural
it	intratracheal
iv	intravenous
LH	lutheinising hormone
MAC	minimal alveolar concentration
MFO	mixed function oxidase

NA	not activated
PNS	peripheral nervous system
po	*per os* (= oral)
RBC	red blood cells
RLiA	rat liver activated
SCE	sister chromatid exchange
sc	subcutaneous
UDS	unscheduled DNA-synthesis

Statistical terms

GM	geometric mean
OR	Odds Ratio
RR	relative risk
SD	standard deviation
SEM	standard error of mean
SMR	standard mortality ratio

Analytical methods

AAS	atomic absorption spectroscopy
BEEL	biological equivalent exposure limit
BEI	biological exposure index
BEM	biological effect monitoring
BM	biological monitoring
ECD	electron capture detector
EM	environmental monitoring
FID	flame ionisation detector
GC	gas chromatography
GLC	gas liquid chromatography
GSC	gas solid chromatography
HPLC	high performance liquid chromatography
IR	infrared
MS	mass spectrometry
NMR	nuclear magnetic resonance
PAS	personal air sampling
TLC	thin layer chromatography
UV	ultraviolet

Additional abbreviations in the present report

ATP	adenosine s'-triphosphate
HCN	hydrogen cyanide
KCN	potassium cyanide
NaCN	sodium cyanide
SCN^-	thiocyanate

Annex **F**

DECOS-documents

DECOS has produced documents on the following substances. To be ordered from the Health Council of the Netherlands:

Aanpassing van grenswaarden bij flexibele werktijden	2001/06OSH
Acetone cyanohydrin	1995/05WGD
p-Aramid fibres	1997/07WGD
Azathioprine	1999/04OSH
Aziridine (ethyl imine)	2000/13OSH
Azobisisobutyronitril	2002/01OSH
1,2,3-Benzotriazole	2000/14OSH
Bisphenol A and its diglycidylether	1996/02WGD
Bromoethane	1998/10WGD
1,2-and t-Butanol	1994/10WGD
n-, iso-, sec-, tert-Butylacetaten	2001/03OSH
β-Butyrolactone	1999/05OSH
Cadmium and inorganic cadmium compounds	1995/04WGD
Calculating cancer risk	1995/06WGD
Carbadox	1999/06OSH
Carbon disulphide	1994/08
Chlorine dioxide	1995/07WGD
p-Chloroaniline	1998/09WGD
4-Chloro-o-toluidine	1998/08WGD
Chlorotrimethylilane	2001/05OSH
Chromium and its inorganic compounds	1998/01WGD
Chromium VI and its compounds	2001/01OSH
Cresols	1998/15WGD

Copper sulphate	1999/01OSH
1996-1997 WGD-rapporten/1996-1997 DECOS reports	1999/01WGD
1,2-Dibromoethane	1999/07OSH
1,2-Dichloroethane	1997/01WGD
Diethylsulphate	1999/08/OSH
Diglycidyl resorcinol ether	1999/09OSH
Diphenylamine	1997/05WGD
<Titeladv>	1998/03WGD
Epichlorohydrin (1-Chloro-2,3-epoxypropane)	2000/10OSH
1,2-Epoxybutane	1998/11WGD
1,2-Ethanediamine	1996/03WGD
Ethyleneglycol ethers	1996/01WGD
Ethylene oxide	2001/11OSH
Ethylene thiourea	1999/03OSH
Formamide and dimethylformamide	1995/08WGD
Hydrazinoethanol, phenylhydrazine, isoniazid, maleic hydrazide	1997/03WGD
Isopropyl acetate	1997/04WGD
Lactate esters	2001/04OSH
Lindane	2001/07OSH
Man made mineral fibers	1995/02WGD
Manganese and its compounds	2001/02OSH
2-Methylaziridine (propylene imine)	1999/10OSH
Methyl Methacrylate	1994/09
Methacrylates. Ethyl methacrylate, n-butyl methacrylate and isobutyl methacrylate	1994/11
Methyl-t-butylether	1994/23
Methyl chloride	1995/01WGD
4,4'-Methylene bis (2-Chloroaniline)	2000/09OSH
4,4'-Methylene dianiline	2000/11OSH
Metronidazole	1999/11OSH
2-Nitropropane	1999/13OSH
N-Nitrosodimethylamine (NDMA)	1999/12OSH
2-Nitrotoluene	1998/12WGD
Pentaerythritol	1997/06WGD
Phenol	1996/04WGD
o-Phenylenediamine	1998/06WGD
Piperidine	1997/08WGD
Procarbazine hydrochloride	1999/14OSH
1- and 2-Propanol	1994/24
Propylene oxide	1997/02WGD
Ronidazole	1998/05WGD
Styrene	1998/07WGD
Styrene	2001/08OSH
Quartz	1998/02WGD
Toluene	2001/09OSH
1,1,1-Trichloroethane	1995/03WGD
1,2,3-Trichloropropane	1994/25
1,2,3-Trichloropropane	1998/14WGD
Urethane (ethyl carbamate)	2000/12OSH

Vinylbromide	1999/15OSH
Xylene	2001/10OSH
Wood dust	1998/13WGD