Cyanides of Hydrogen, Sodium and Potassium, and Acetone Cyanohydrin (CAS No. 74-90-8, 143-33-9, 151-50-8 and 75-86-5)

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CONTENTS - VOLUMES I AND II

EXECUTIVE SUMMARY

This report has been produced as part of the ECETOC Joint Assessment of Commodity Chemicals (JACC) programme. It presents a critical evaluation of the toxicity and ecotoxicity data on hydrogen cyanide (HCN), sodium and potassium cyanides (NaCN and KCN) and acetone cyanohydrin (ACH). Most of these cyanides under physiological and environmental conditions will be present as HCN, which is the common toxic species (ACH dissociates into acetone and HCN). HCN (liquid or gas) and ACH (liquid) are used as chemical intermediates. NaCN and KCN (solids) are mainly used in silver and gold mining and in electroplating. All of these forms of cyanide are soluble in water.

Local releases of cyanide into water will be removed by volatilisation within a few days. Cyanide in water can exist as free HCN, or as complexes and salts, which may dissociate again to free HCN or adsorb onto sediment. Elimination of complex cyanides may take longer than free cyanide. In the global environment, cyanide is distributed to air and water. The main source of HCN in the atmosphere is the combustion of biomass. Airborne HCN undergoes slow photolysis, but the major part is absorbed into the oceans, where cyanide is removed by chemical and/or biological degradation. The overall atmospheric lifetime of HCN is 5 to 6 months.

Aquatic organisms (fish, invertebrates and algae) are very sensitive to cyanides. In the laboratory, concentrations as low as a few µg/l were found to be toxic. Water birds survived higher concentrations.

In mammals, cyanides (HCN) are very toxic regardless of the route of entry. HCN is rapidly absorbed and distributed within the body, and blocks the function of organs with great oxygen demand such as brain, heart and testes. Cyanides can also be lethal upon skin contact (even if only a small area is exposed) or following eye contact. There is no concern on the reproductive toxicity, and mutagenic or genotoxic activity of cyanides. No reliable carcinogenicity studies in animals exist (the quick onset of toxicity renders such studies impractical).

The dose rate is a critical factor in cyanide poisoning. The total amount of cyanide that can be tolerated is greater when the dose rate is below the detoxification rate. In long-term animal studies, where the dose is delivered over an extended period (such as in drinking water or in the diet) rather than in a bolus, no adverse effects were seen at levels markedly above the acute lethal dose.

Cyanide is normally detoxified in the body and eliminated as thiocyanate (in urine). Though less toxic than cyanide, chronic exposure to thiocyanate can exacerbate the effects of low iodine content in the diet and result in goitre. This is endemic in peoples who consume cassava as a

significant part of their diet, e.g. populations of Central Africa. Cassava is rich in cyanogenic glucosides.

Worker health studies with cyanides are inadequate for determining a no-adverse effect level in humans. Other studies (nutritional, epidemiological and clinical) indicate the absence of thiocyanate-mediated toxicity to the thyroid gland from daily doses equivalent to an occupational exposure (8-hour) of 7.5 mg CN^-/m^3 (time-weighted average) for humans with sufficient dietary iodine and normal kidney function. The acutely toxic cyanide concentration that can be tolerated by humans may be of the same order of magnitude. Sensitive sub-populations would include individuals with insufficient dietary iodine, insufficient thiosulphate supply (e.g. in the case of malnutrition) and impaired renal function. Tolerable exposure levels for cyanide salt dust may be lower (maximum 2 times, assuming 100% absorption).

Neurological disorders are known to occur in populations consuming food containing cyanogenic glucosides (e.g. cassava), particularly in combination with poor nutrition (when cyanide detoxification is impaired). There is no causal link between occupational exposure to cyanide and subjective symptoms of neurotoxicity. Parkinson-like symptoms have been reported in cases of acute cyanide poisoning (e.g. attempted suicide). Repeated low-dose exposure to cyanide has no such effects.

During the preparation of this document, draft versions were made available to SCOEL [a] and IPCS CICAD [b]. A hazard/risk assessment will be required under current OECD and proposed EU schemes [c,d].

[a] Scientific Commmittee on Occupational Exposure Limits of the EC
[b] International Programme on Chemical Safety, Concise International Chemical Assessment Documents
[c] OECD Existing Chemicals Programme
[d] EU Registration, Evaluation and Authorisation of Chemicals

THE ECETOC SCHEME FOR THE JOINT ASSESSMENT OF COMMODITY CHEMICALS

This report has been produced as part of the ECETOC Joint Assessment of Commodity Chemicals (JACC) programme for preparing critical reviews of the toxicology and ecotoxicology of selected existing industrial chemicals. In the programme, commodity chemicals (i.e. those produced in large tonnage by several companies and having widespread and multiple uses) are jointly reviewed by experts from a number of companies with knowledge of the chemicals. Only the chemical itself is considered in a JACC review; products in which it appears as a component or an impurity are not normally taken into account.

This document presents a critical evaluation of the toxicology, ecotoxicology, environmental fate and impact of the cyanides of hydrogen, sodium and potassium, and acetone cyanohydrin (CAS No. 74-90-8, 143-33-9, 151-50-8 and 75-86-5).

Special abbreviations, including symbols, units and prefixes, used in this report are explained in Appendix A.

Where relevant, the Task Force has graded the (eco)toxicological studies by means of a ‘code of reliability’ (CoR) (Appendix B) to reflect the degree of confidence that can be placed on the reported results.

1. SUMMARY AND CONCLUSIONS

This report reviews the available physico-chemical, ecotoxicity and toxicity data on hydrogen cyanide (HCN), sodium and potassium cyanides (NaCN and KCN) and acetone cyanohydrin (ACH). These substances are reviewed together because the cyanide anion (CN^-) or HCN is the common toxic species of the reviewed substances. As HCN is a relatively weak acid (dissociation constant Ka ≈ 10^{-9}), most of the cyanide under physiological and environmental conditions (pH ≈ 5 - 8) will be present as HCN.

Cyanide plays an important role in pre-biotic chemistry and the origin of life. Cyanide polymerisation and hydrolysis to formamide under specific conditions (cold environment where cyanide concentration is sufficiently high) is most probably responsible for the formation of the first nucleic and amino acids on earth (Miyakawa *et al*, 2002a,b). Cyanogenic molecules are found in a variety of organisms including many plants, e.g. apple seeds, peach pits, cassava.

HCN is a clear, volatile liquid or gas. It completely dissolves in water. NaCN and KCN are water soluble, white crystalline solid salts. ACH is a clear liquid that dissociates into acetone and HCN. ACH vapour decomposes rapidly into HCN and acetone. ACH in water undergoes rapid hydrolysis to HCN and acetone.

HCN, NaCN, KCN and ACH are produced in amounts greater than 100 kt per year worldwide. HCN is mainly used as an intermediate in the chemical industry for the production of chemicals such as adiponitrile, methyl methacrylate, cyanuric chloride or cyanide salts. The main areas of use for NaCN and KCN are gold and silver leaching in mining, electroplating, metal surface hardening and synthesis of organic chemicals. ACH is mainly used as an intermediate for the synthesis of methacrylic acid, methyl methacrylate, and other methacrylates.

When released into the environment, cyanide will distribute mainly to the atmosphere and water. The main source of HCN in the atmosphere is the combustion of biomass. Concentrations in the troposphere over the northern hemisphere amounted to 160 ppt by volume (≈ 180 ng/m^3). HCN will undergo photodegradation in the troposphere with a lifetime of one to several years (depending on the hydroxyl radical concentration), but the oceans act as a major and rapid sink for atmospheric HCN. This leads to an estimated overall atmospheric lifetime of 5.0 or 6.2 months. The oceanic sink is caused by a permanent under-saturation, probably due to chemical and/or biological degradation of cyanide. In the aquatic environment, cyanide can exist in numerous forms including free cyanide (HCN), cyanide complexes and less soluble cyanide salts. The fate and behaviour of the different cyanide species depends largely on their dissociation to free cyanide and their ability to adsorb onto sediment. Photolysis of cyanide complexes can liberate cyanide under the influence of sunlight. Volatilisation is expected to be an important and potentially dominant elimination process for cyanide released directly into water. Biodegradation,

complexation with subsequent adsorption onto sediment, and to a lesser extent photolysis and abiotic degradation, are additional possible routes of elimination. The half-life of free cyanide is mainly governed by volatilisation. It can be in the range of a few days to weeks depending on the wind speed and altitude, the temperature, the surface area, and the surface to volume ratio of the water body. The half-life of complex cyanides may be much longer.

Cyanide is acutely very toxic to aquatic organisms. Median lethal and/or effect concentration (LC_{50}/EC_{50}) values ranged from about 20 to 170 µg CN^-/l for fish, 2 to 1,000 µg/l for invertebrates and 45 to 500 µg/l for algae. Chronic no-observed effect concentration (NOEC) values were between < 1 and 5 µg CN^-/l for fish, 5 to 30 µg/l for invertebrates and 4 to 265 µg/l for algae. Probabilistic analysis of the large amount of available aquatic toxicity data led to the derivation of an acute tolerable concentration of 5 µg/l free cyanide and a long-term predicted no-effect concentration (PNEC) of 1 µg/l free cyanide for the aquatic environment.

For birds a tolerable concentration of 10 mg CN^-/l was derived.

In mammals, cyanide is rapidly absorbed in the form of HCN following oral, dermal or inhalation exposure. Cyanides are very toxic by all routes of entry. The mechanism of toxicity is by inhibition of oxygen utilisation by tissues; the most sensitive organs are those with the greatest oxygen demand such as brain, heart and testes. In humans, the acute lethal dose is approximately 1.5 mg/kgbw following oral uptake. The acute inhalation toxicity is a function of the body weight and the time of exposure. Using probit analysis of the acute inhalation data in different species, a human LC_{50} value of 202 mg/m^3 (180 ppm) and an LC_{01} of 88 mg/m^3 (78 ppm) were derived, both following 60 minutes of exposure. The lethal dose by the dermal route will depend upon the area of skin exposed. A dose of approximately 100 mg/kgbw is lethal even if only a small area of skin is contacted. Acutely toxic levels might also be achieved following eye contact.

Neurological disorders have been reported in populations consuming diets with high cyanogenic glucoside content (e.g. cassava). These populations are thought to have an increased sensitivity to cyanide due to poor nutrition and an associated impaired ability to detoxify cyanide. Occupational studies report a wide range of subjective symptoms suggestive of neurotoxicity that are not clearly related to cyanide exposure. A few published cases link cyanide exposure with Parkinson-like symptoms. These are all related to acute over-doses of cyanide (mostly in connection with attempted suicides) that were treated in a comatose stage. There is no indication from the available data that repeated low-dose exposure to cyanide could have similar effects.

The direct toxicity of cyanide prevents the conduct of studies on reproductive toxicity, and renders the available studies irrelevant. ACH showed no evidence of teratogenicity following gavage dosing of rats up to and including doses that produced maternal toxicity. In male and female fertility studies in rats, inhaled ACH showed no reproductive effects up to the onset of

acute toxicity (local irritant effects and systemic lethality), as indicated in repeated-dose inhalation studies. Therefore, although cyanide is overtly toxic to the reproductive system, there is no reason to suspect that this system is any more sensitive than are other organ systems.

Valid data are available for all genetic endpoints and there is no indication of mutagenic or genotoxic activity of cyanide. Although there are no reliable data on carcinogenicity in animals, the steep dose-response relationship would render the conduct of such a study impractical.

Cyanide is detoxified in the body through the formation and elimination in the urine of thiocyanate. Although less toxic than cyanide, thiocyanate can, in situations of chronic exposure (such as those occurring in cassava eating populations in Central Africa), exacerbate the effects of low iodine content in the diet resulting in commonly observed hyperthyroidism (goitre). Thiocyanate is a competitive inhibitor of iodide absorption by the thyroid gland and causes a decreased output of thyroxin by the thyroid. Re-adjustment to the original output of thyroxin requires an increase in thyroid mass (volume) brought about by increased secretion of thyroid stimulating hormone by the pituitary gland. Thyroid mass changes within 50% of normal are regarded as being within the physiological range with an increase of 500% or more being considered as goitre.

The toxicodynamics of cyanide poisoning in animals are complex and determined by a number of factors. These include the dose and rate of delivery of cyanide, the steep dose-response for acute toxicity, the rate and total capacity for detoxification (thiocyanate formation) and the rate of elimination of thiocyanate. In acute poisoning scenarios, the rate of delivery of cyanide can exceed the detoxification capacity resulting in overt acute toxicity. Whereas in chronic exposure scenarios, or where the rate of delivery is maintained within the detoxification capacity, this can be avoided. Consequently, it is possible to achieve a higher cumulative dose of cyanide when delivery is over a longer period than if it is delivered in a single bolus. This phenomenon is apparent in several of the mammalian toxicity studies reported with cyanides and is important in establishing a chronic no-observed adverse effect level (NOAEL) of relevance for humans. For example, in long-term dietary and drinking-water studies with cyanide in rats and mice, the NOAELs were 10.4 to 25.6 mg CN^-/kgbw/d. This is markedly above the median lethal dose (LD_{50}) of 3.3 to 3.9 mg CN^-/kgbw.

In 90-day guideline studies in rats administered cyanide via the drinking water (Hébert, 1993) or by inhalation (Monsanto, 1984), a NOAEL in the range of 10.4 to 12.5 mg CN^-/kgbw/d is indicated. This value is approaching, but below, the steep dose-response curve for acute lethality in this species and slightly below the observed NOAEL of 25.6 mg CN^-/kgbw/d in mice observed in a 90-day guideline drinking water study (Hébert, 1993). Lower NOAELs have been reported for dogs and miniature pigs but these studies are believed to be confounded by acute toxicity and

dietary complications. Generally, dogs tend to be more sensitive because of lower tissue levels of the enzyme rhodanese.

Available worker health studies involving occupational exposure to cyanides are too limited and lack essential detail regarding nutritional and iodine status. This renders them unreliable as a basis for setting a NOAEL for humans. Nutritional, epidemiological (morbidity) and clinical volunteer studies with cyanides, in contrast, typically include appropriate measurement of relevant clinical and dietary parameters such as dietary protein and iodide, serum and urinary thiocyanate, and smoking habits. These indicate the absence of adverse effects mediated via thiocyanate from daily doses equivalent to an 8-hour time-weighted average (TWA) exposure (e.g. occupational conditions) of 7.5 mg CN^-/m^3 for humans with sufficient dietary iodine and normal renal function. An analysis of the acute toxicity data and the human cyanide detoxification rates suggests that the tolerable concentration in humans with regard to cyanide-mediated acute toxicity may be of the same order of magnitude.

Sensitive sub-populations would include individuals with insufficient dietary iodine, insufficient thiosulphate supply (e.g. in the case of malnutrition) or impaired renal function. Iodine may need to be supplemented to restore and maintain the iodine-thiocyanate ratio (measured in urine, concentrations expressed in µg/mg) to above 3 to 4.

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13.3 Databases consulted

Initial literature searches were made for CAS 74-90-8, 143-33-9 and 151-50-8 in Dimdi: Aquire, Chemline, Terretox (1990 - 1996); the references were included in updated IUCLID data sets (Degussa, 2000d,e,f). Three other IUCLIDs, on ACH and HCN, were also available (Ineos Acrylics, 1994a,b; Degussa, 1998).

The literature from 1997 onwards was searched in May 2000 for HCN, NaCN and KCN (CAS 74-90-8, 143-33-9 or 151-50-8) in Dimdi/Superbase, including Emtrain, Aidsline, Cancerlit, Healthstar, Medline, Toxline, Biotechnoba, Cab Abstrac, Toxbio, Ipa, Embase, Biosis Prev and Toxcas (1997), and also in May 2000, in Cis/Sanss all databases such as TscaInv, OhmTads, Merck, Rtecs, Phytotox, Genetox, Aquire, Dermal, Iris, Ishow, Biolog and Datalog.

In March 2001, NLM Toxline was searched for ACH (CAS 75-86-5) in Biosis, Caplus, Embase, MedLine, Toxline and Hsdb (2000). Specific searches were conducted for Parkinson's disease and cyanides poisoning on Dimdi-Medline. Additional references were found for HCN, NaCN in Micromedex-Meditext (1999) and Hsdb (1999).

The general literature search was updated in August 2003.

In 2003, a research was made of the US-EPA Ecotox database for aquatic effect data on cyanide, HCN, NaCN, KCN and ACH (US-EPA, 2003).

APPENDIX A: SPECIAL ABBREVIATIONS, SYMBOLS, UNITS AND PREFIXES

≈	Approximately
~	Estimated
↓	Decrease, reduction
↑	Increase, elevation
<	Less than
µ-	Micro (10^{-6})
>	More than
≥	More than or equal to
–ve	Negative
+ve	Positive
√	Square root
×	Times, fold

ACH	Acetone cyanohydrin
ADP	Adenosine diphosphate
ALT	Alanine aminotransferase
APV	2-Amino-5-phosphonovalerate
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
BAF	Bioaccumulation factor
BCF	Bioconcentration factor
BOD	Biological oxygen demand
bw	Body weight
C	Concentration
CAS	Chemical Abstracts Service
CN^-	Cyanide anion
CO	Carbon monoxide
CoR	Code of reliability
d	Day
DIN	Deutsches Institut für Normung
EAT	ECETOC aquatic toxicity (database)
EC	European Commission
EC_{50}	Median effect concentration
EINECS	European inventory of existing commercial chemical substances
EPER	European pollutant emission register
ET_{50}	Median effective time
G-	Giga (10^9)
GC	Gas chromatography

GSH	Glutathione
h	Hour
HC_5	Hazardous concentration for 5% of species
HCN	Hydrogen cyanide
hPa	Hectopascal
HPLS	High performance liquid chromatography
IC_{25}	Inhibition concentration that causes a 25% reduction
i.p.	Intraperitoneal
IP_3	Inositol triphosphate
i.v.	Intravenous
ISO	International Organization for Standardization
IUPAC	International Union of Pure and Applied Chemistry
J	Joule
k-	Kilo (10^3)
KCN	Potassium cyanide
K_{oc}	Partition coefficient (organic carbon/water)
K_{ow}	Partition coefficient (octanol/water)
l	Litre
LAD	Laboratory animal diet
LC_x	Lethal concentration to x% of the population
LC_{50}	Median lethal concentration
LC_{100}	Absolute lethal concentration
LD_{50}	Median lethal dose
LETC	Lethal threshold concentration
LOEC/LOEL	Lowest-observed effect concentration or level
ln	Natural logarithm
log	Common logarithm
LT_{50}	Median survival time
M-	Mega (10^6)
m	Metre
m-	Milli (10^{-3})
MATC	Maximum acceptable toxicant concentration
min	Minute
MK-801	(+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohept-5,10-imine maleate
mol	Mole
MS	Mass spectrometry
Mw	Molecular weight (mass)
n	Number
n-	Nano (10^{-9})

˙OH	Hydroxyl radical
NaCN	Sodium cyanide
NAD(P)H	Reduced nicotanimide adenine dinucleotide (phosphate)
NMDA	N-methyl-D-aspartate
NO	Nitric oxide
No.	Number
NOAEL	No observed adverse effect level
NOEC	No observed effect concentration
p-	Pico ($10^{-12)}$
PG	Packing group
pH	–log (H^+ concentration), measure of acidity
pKa	–log (acidity constant), measure of extent of acidity
PKC	Phosphokinase C, protein kinase C
PLA2	Phospholipase A2
PNEC	Predicted no effect concentration
ppb	Parts per billion (10^9), by volume
ppm	Parts per million (10^6), by volume
ppt	Parts per trillion (10^{12}), by volume
ROS	Reactive oxygen species
R-	Risk
s	Second
S-	Safety
S9	Supernatant of centrifuged 9,000 × g liver homogenate
SAA	Sulphur-amino acid
SAFARI	Southern Africa regional science initiative
s.c.	Subcutaneous
SCN^-	Thiocyanate anion
sp.	Species
SOD	Superoxide dismutase
SSD	Species sensitivity distribution
t	Tonne, time
T3	Tri-iodothyronin
T4	Thyroxin
TRACE-P	Transport and chemical evolution in the Pacific ocean
TRH	Thyrotropin releasing hormone
TRI	Toxics release inventory
TSH	Thyroid stimulating hormone
TWA	Time-weighted average
U	Unit
WAD	Weak acid dissociable

wk	Week
y	Year

APPENDIX B: CRITERIA FOR RELIABILITY CATEGORIES

Adapted from Klimisch *et al* (1997)

Code of Reliability (CoR)	Category of reliability
1	Reliable without restriction
1a	'Good laboratory practice' guideline study (OECD, EC, EPA, FDA, *etc.*)
1b	Comparable to guideline study
1c	Test procedure in accordance with national standard methods (AFNOR, DIN, *etc*.)
1d	Test procedure in accordance with generally accepted scientific standards and described in sufficient detail
2	Reliable with restrictions
2a	Guideline study without detailed documentation
2b	Guideline study with acceptable restrictions
2c	Comparable to guideline study with acceptable restrictions
2d	Test procedure in accordance with national standard methods with acceptable restrictions
2e	Study well documented, meets generally accepted scientific principles, acceptable for assessment
2f	Accepted calculation method
2g	Data from handbook or collection of data
3	Not reliable
3a	Documentation insufficient for assessment
3b	Significant methodological deficiencies
3c	Unsuitable test system
4	Not assignable
4a	Abstract
4b	Secondary literature
4c	Original reference not yet available
4d	Original reference not translated
4e	Documentation insufficient for assessment

APPENDIX C: CONVERSION FACTORS FOR VAPOUR CONCENTRATIONS IN AIR

Conversion factors for vapour concentrations in air can be calculated from the molar volume of an ideal gas at 0°C: 22.4136 litre.

$$1\ mg/m^3 = 22.4136/Mw \times 1{,}013.25/P \times (273 + T)/273\ ppm \quad \text{(Eq. C.1)}$$

$$1\ ppm = Mw/22.4136 \times P/1{,}013.25 \times 273/(273 + T)\ mg/m^3 \quad \text{(Eq. C.2)}$$

Where Mw = molecular weight (mass), T = temperature (°C) and P = pressure (hPa).

For European standard conditions, 20°C and 1,013.25 hPa (= 1 atm = 760 mm Hg), the formulae become:

$$1\ mg/m^3 = 24.0556/Mw\ ppm \quad \text{(Eq. C.3)}$$

$$1\ ppm = Mw/24.0556\ mg/m^3 \quad \text{(Eq. C.4)}$$

In the USA and other countries 25°C is used, and the formulae are:

$$1\ mg/m^3 = 24.4661/Mw\ ppm \quad \text{(Eq. C.5)}$$

$$1\ ppm = Mw/24.4661\ mg/m^3 \quad \text{(Eq. C.6)}$$

APPENDIX D: SERUM AND URINARY THIOCYANATE LEVELS AFTER ORAL ADMINISTRATION OF CYANIDES

Table D.1 presents blood (serum) and urinary thiocyanate levels whenever they were available from the repeated-dose experiments discussed in Section 8.3.1 and 8.3.3.

Table D.1: Serum and urinary thiocyanate levels

Duration, species (route) / Dose (mg CN^-/kgbw) [a]	Cyanide compound / Sampling time	Thiocyanate level		Remark	Reference
		In serum	In urine		
13 wk, rat (drinking water)	**NaCN**		**(µg SCN^-/ml)**	**Urinary volume (ml/16 h)**	**Hébert, 1993**
(0)	d 8	Not stated	5.1 ± 2.0	3.9 ± 0.9	
	d 22		12.2 ± 3.1	7.6 ± 1.6	
	d 43		7.4 ± 2.7	8.3 ± 1.3	
	d 88		7.5 ± 2.5	9.2 ± 2.1	
(0.16)	d 8	Not stated	6.1 ± 1.9	4.8 ± 0.7	
	d 22		15.7 ± 4.9	4.7 ± 1.4	
	d 43		7.8 ± 1.7	8.4 ± 0.9	
	d 88		5.4 ± 1.6	6.8 ± 0.8	
(0.48 - 0.53)	d 8	Not stated	9.7 ± 1.0 [b]	3.9 ± 0.6	
	d 22		21.0 ± 3.3	5.2 ± 1.2	
	d 43		25.5 ± 6.9 [c]	8.9 ± 2.8	
	d 88		12.2 ± 1.8	7.1 ± 1.6	
(1.4 - 1.7)	d 8	Not stated	28.3 ± 2.2 c	2.8 ± 0.4	
	d 22		39.7 ± 6.9 c	6.6 ± 1.1	
	d 43		48.4 ± 8.4 c	7.8 ± 1.1	
	d 88		40.9 ± 4.0	5.5 ± 0.6	

Table D.1: Serum and urinary thiocyanate levels (cont'd)

Duration, species (route) / Dose (mg CN^-/kgbw) [a]	Cyanide compound / Sampling time	Thiocyanate level		Remark	Reference
		In serum	In urine		
13 wk, rat (drinking water) (cont'd)	**NaCN**		**(µg SCN^-/ml)**	**Urinary volume (ml/16 h)**	**Hébert, 1993**
(4 - 4.3)	d 8	Not stated	100.7 ± 9.9 [c]	4.8 ± 2.8	
	d 22		111.8 ± 9.8 [c]	6.9 ± 2.8	
	d 43		112.1 ± 15.5 [c]	6.4 ± 3.3	
	d 88				
(12.5)	d 8	Not stated	202.0 ± 10.8 [c]	1.3 ± 0.3 [c]	
	d 22		155.1 ± 39.3 [c]	2.8 ± 0.8 [c]	
	d 43		224.7 ± 55.5 [c]	2.8 ± 0.4 [c]	
	d 88		242.4 ± 31.7 [c]	3.3 ± 0.6 [c]	

Table D.1: Serum and urinary thiocyanate levels (cont'd)

Duration, species (route) / Dose (mg CN^-/kgbw) [a]	Cyanide compound / Sampling time	Thiocyanate level				Reference
		In serum		In urine		
13 wk, rat (drinking water)	**KCN**	**(µmol SCN^-/ml)**	**(µg SCN^-/ml) [a]**	**(µmol SCN^-/kgbw/24 h)**	**(µg/kgbw SCN^-/24 h) [a]**	**Leuschner *et al*, 1991**
0	wk1	0.011	(0.64)			
	wk 3	0.019	(1.10)			
	wk 5	0.036	(2.09)			
	wk 6	-	-	0.82	(47.6)	
	wk 7	0.054	(3.14)			
	wk 9	0.049	(2.85)			
	wk 11	0.036	(2.09)			
	wk 13	0.039	(2.3)	0.77	(44.7)	
16	wk 1	0.17	(9.87)			
	wk 3	0.23	(13.4)			
	wk 5	0.32	(18.6)			
	wk 6	-	-	68.6	(3,980)	
	wk 7	0.26	(15.1)			
	wk 9	0.23	(13.4)			
	wk 11	0.32	(18.6)			
	wk 13	0.19	(11.0)	60.1	(3,490)	

Table D.1: Serum and urinary thiocyanate levels (cont'd)

Duration, species (route) / Dose (mg CN^-/kgbw) [a]	Cyanide compound / Sampling time	Thiocyanate level				Reference
		In serum		In urine		
13 wk, rat (drinking water) (cont'd)	**KCN**	**(µmol SCN^-/ml)**	**(µg SCN^-/ml) [a]**	**(µmol SCN^-/kgbw/24 h)**	**(µg SCN^-/kgbw/24 h) [a]**	**Leuschner *et al*, 1991**
32	wk 1	0.28	(16.3)			
	wk 3	0.27	(15.7)			
	wk 5	0.42	(24.4)			
	wk 6	-	-	142.7	(8,290)	
	wk 7	0.34	(19.8)			
	wk 9	0.37	(21.5)			
	wk 11	0.42	(24.4)			
	wk 13	0.40	(23.2)	151.0	(8,770)	
64/56	wk 1	0.24	(13.9)			
	wk 3	0.88	(51.1)			
	wk 5	0.68	(39.5)			
	wk 6	-	-	197.5	(11,470)	
	wk 7	0.45	(26.1)			
	wk 9	0.34	(19.8)			
	wk 11	0.46	(26.7)			
	wk 13	0.48	(27.9)	443.6	(25,770)	

Table D.1: Serum and urinary thiocyanate levels (cont'd)

Duration, species (route) / Dose (mg CN^-/kgbw) [a]	Cyanide compound / Sampling time	Thiocyanate level			Remark	Reference
		In serum		In urine		
14 d, rat (drinking water)	**KCN**	**(µmol SCN^-/ml)**	**(µg SCN^-/ml) [a]**			**Sousa *et al*, 2002**
(0)	d 15	0.0568 ± 0.0059	(3.299 ± 0.343)	Not stated		
(0.12)		0.0757 ± 0.0077	(4.397 ± 0.447)			
(0.36)		0.1142 ± 0.0172	(6.633 ± 0.999)			
(1.2)		0.1539 ± 0.0111	(8.939 ± 0.645)			
(3.6)		0.1332 ± 0.0110	(7.736 ± 0.639)			
56 d, rat (diet)	**KCN**	**(µmol SCN^-/ml) [a]**	**(µg SCN^-/ml)**		**Urinary excretion (mg/100 mg food)**	**Tewe and Maner, 1982**
(0)	Not stated	(0.291 ± 0.014)	16.9 ± 0.8	Not stated	1.96 ± 0.05 in first week	
(40) [d]	d 56	(0.470 ± 0.024)	27.3 ± 1.4	Not stated	5.34 ± 0.53	
14 wk, rat (diet)	**KCN**	**(µmol/ml) [a]**	**(µg/ml)**			**Olusi *et al*, 1979**
(0)	Not stated	(2.20 ± 0.13)	128 ± 7.7	Not stated		
(1,000)		(3.79 ± 0.39)	220 ± 22.6			
(2,000)		(5.68 ± 0.67)	330 ± 38.7			

Table D.1: Serum and urinary thiocyanate levels (cont'd)

Duration, species (route) / Dose (mg CN^-/kgbw) [a]	**Cyanide compound / Sampling time**	**Thiocyanate level**		**Remark**	**Reference**
		In serum	**In urine**		
11.5 months, rat (diet)	**KCN**			**Urinary excretion (µg/g food)**	**Philbrick *et al*, 1979**
(0) normal diet	4 months	Not stated	Not stated	9 ± 1	
	11 months			12 ± 3	
(40)	4 months			505 ± 44	
	11 months			219 ± 27	
(0) restricted diet	4 months			9 ± 1	
	11 months			5 ± 1	
(54)	4 months			415 ± 27	
	11 months			202 ± 49	

Table D.1: Serum and urinary thiocyanate levels (cont'd)

Duration, species (route) / Dose (mg CN^-/kgbw) [a]	Cyanide compound / Sampling time	Thiocyanate level				Reference
		In serum		In urine		
14 wk, dog (oral feed)	**NaCN**	**(µmol/ml)**	**(µg/ml)**	**(µmol/ml)**	**(µg/ml)**	**Kamalu, 1991, 1993; Kamalu and Agharanya, 1991**
(0)	All sampling times	0	0	0 [d]	(0)	
(0.93)	wk 1	0.080 ± 0.007	(4.64 ± 0.41[e])	132.0 ± 0.45	(7,656 ± 26.1 [f])	
	wk 3	0.085 ± 0.005	(4.93 ± 0.29 [e])	84.4 ± 19.12	(4,895 ± 1109 [f])	
	wk 5	Not stated	-	93.47 ± 13.87	(5,421 ± 805 [f])	
	wk 7	Not stated	-	50.05 ± 13.25	(2,903 ± 769 [f])	
	wk 14	0.119 ± 0.019	(6.9 ± 1.1 [e])	59.10 ± 15.04	(3,428 ± 872 [f])	

Table D.1: Serum and urinary thiocyanate levels (cont'd)

Duration, species (route) / Dose (mg CN^-/kgbw) [a]	Cyanide compound / Sampling time	Thiocyanate level			Remark	Reference
		In serum		In urine		
56 d, pig	**KCN**	**(µmol/ml) [a]**	**(µg/ml)**		**Urinary excretion (µg/g food)**	**Tewe and Maner, 1980**
(0)		(0.069 - 0.15)	4 - 9 [g]	Not stated	7.7 mg/kg food intake	
50 mg CN^-/100 mg food [h]						
Protein-deficient + I	14 d	(0.14)	8	Not stated	13.7 ± 4.7	
	28 d	(0.22)	13			
	42 d	(0.26)	15			
	56 d	(0.17)	10			
Protein-deficient – I	14 d	(0.21)	12		12.3 ± 2.9	
	28 d	(0.21)	12			
	42 d	(0.29)	17			
	56 d	(0.21)	12			
Sufficient protein + I	14 d	(0.22)	13		15.5 ± 2.2	
	28 d	(0.24)	14			
	42 d	(0.38)	22			
	56 d	(0.31)	18			
Sufficient protein – I	14 d	(0.22)	13		12.8 ± 1.6	
	28 d	(0.36)	21			
	42 d	(0.38)	22			
	56 d	(0.31)	18			

Table D.1: Serum and urinary thiocyanate levels (cont'd)

Duration, species (route) / Dose (mg CN^-/kgbw) [a]	Cyanide compound / Sampling time	Thiocyanate level			Remark	Reference
		In serum		In urine		
5 months, goat (milk and gavage)	**KCN**	**(µmol/l)**	**(µg/ml) [a]**			**Soto-Blanco *et al*, 2001b**
0	d 0	15.89 ± 2.41	(923 ± 140)	Not stated		
	d 77	12.11 ± 1.56	(703 ± 91)			
	d 153	4.94 ± 0.74	(287 ± 43)			
0.12	d 0	16.91 ± 3.93	(982 ± 228)			
	d 77	12.48 ± 2.46	(725 ± 143)			
	d 153	8.97 ± 0.43	(521 ± 25)			
0.24	d 0	19.40 ± 2.86	(1,127 ± 166)			
	d 77	11.14 ± 1.64	(647 ± 95)			
	d 153	10.83 ± 1.41	(629 ± 82)			
0.48	d 0	14.11 ± 3.28	(820 ± 191)			
	d 77	16.91 ± 4.73	(982 ± 275)			
	d 153	11.73 ± 1.88	(681 ± 109)			
1.2	d 0	17.84 ± 1.32	(1,036 ± 77)			
	d 77	33.55 ± 4.92	(1,949 ± 286)			
	d 153	48.05 ± 7.1	(2,791 ± 412)			

Table D.1: Serum and urinary thiocyanate levels (cont'd)

Duration, species (route) / Dose (mg CN^-/kgbw/d) [a]	Cyanide compound / Sampling time	Thiocyanate level				Reference
		In serum		In urine		
4 wk, rat (inhalation)	**ACH**	**(µmol SCN^-/ml) [a]**	**(µg SCN^-/ml)**	**(µmol SCN^-/ml) [a]**	**(µg SCN^-/ml)**	**Monsanto, 1981d**
(0) M	wk 4	(0.165 ± 0.019)	9.6 ± 1.1	(0.549 ± 0.210)	31.9 ± 12.2	
(0) F		(0.217 ± 0.069)	12.6 ± 4.0	(0.730 ± 0.226)	42.4 ± 13.1	
(1.3) M		(0.232 ± 0.024)	13.5 ± 1.4 [i]	(2.192 ± 0.668)	127.3 ± 38.8	
(1.3) F		(0.391 ± 0.195)	22.7 ± 11.3 [i]	(2.152 ± 0.468)	125.0 ± 27.2	
(4.4) M		(0.226 ± 0.031)	13.1 ± 1.8 [i]	(4.704 ± 1.207)	273.2 ± 70.1 [i]	
(4.4) F		(0.363 ± 0.093)	21.1 ± 5.4 [j]	(6.829 ± 3.061)	396.6 ± 177.8 [i]	
(8.7) M		(0.195 ± 0.048)	11.3 ± 2.8	(9.842 ± 3.571)	571.6 ± 207.4 [i]	
(8.7) F		(0.301 ± 0.076)	17.5 ± 4.4	(9.571 ± 3.106)	555.9 ± 180.4 [i]	
14 wk, rat (inhalation)	**ACH**	**(µmol SCN^-/ml) [a]**	**(µg SCN^-/ml)**	**(µmol SCN^-/ml) [a]**	**(µg SCN^-/ml)**	**Monsanto, 1984**
(0) M	wk 14	(0.96 ± 0.45)	56 ± 26	(0.50 ± 0.77)	29 ± 45	
(0) F		(0.74 ± 0.36)	43 ± 21	(0.017 ± 0.086)	1 ± 5	
(1.8) M		(1.43 ± 0.50)	83 ± 29 [j]	(5.41 ± 3.62)	314 ± 210	
(1.8) F		(1.48 ± 0.31)	86 ± 18 [i]	(0.41 ± 0.34)	24 ± 19.8	
(5.5) M		(1.21 ± 0.38)	70 ± 22	(16.18 ± 9.52)	940 ± 553 [i]	
(5.5) F		(1.45 ± 0.65)	84 ± 38 [i]	(9.64 ± 6.68)	560 ± 388 [i]	
(10.4) M		(1.00 ± 0.59)	58 ± 34	(31.46 ± 13.67)	1,827 ± 794 [i]	
(10.4) F		(0.83 ± 0.45)	48 ± 26	(19.78 ± 11.52)	1,149 ± 669 [i]	

[a] Values in parentheses are converted (Section 8.3.1 and 8.3.3)
[b] $p < 0.05$ Shirley's test
[c] $p < 0.01$ Shirley's test
[d] values taken from animals with normal diet
[e] $p < 0.01$ Duncan's multiple range test
[f] 24-h urine volume not given
[g] From graph in paper
[h] Doses not converted (bw not given) (Table 46)
[i] $p < 0.01$ Dunnet's t-test
[j] $p < 0.05$ Dunnet's t-test

APPENDIX E: REVIEW OF MECHANISTIC STUDIES

E.1 Differential histopathology of brain lesions

Earlier studies focused mainly on cyanide-induced brain lesions and their distribution using histopathology to determine the most sensitive structures of the brain.

Albino rats (males and females from 4 different sources; no further details given) were exposed individually by inhalation to increasing levels and durations of HCN (actual values not stated), adjusted to achieve certain effects. Clinical observations were divided into (i) restlessness and increased activity, (ii) decreased voluntary muscle activity and postural tonus but reaction to stimuli remaining; respiration irregular, (iii) complete loss of motor activity, only very slight reaction to stimuli; regular respiration of moderate depth (frequency of 40 - 80/min), and (iv) no reaction to stimuli; respiration slow and regular, diminishing progressively in amplitude and frequency until death. The authors observed that at a certain level of intoxication characterised by shallow respiration, even if attained very briefly, irreversible damage to the respiratory centre occurred and death could not be prevented by cessation of HCN exposure, although the heart beat was still detectable for some time. When exposure was halted before that stage, the rats went through the four stages described above. Some additional deaths occurred in stage 2, preceded by convulsions and apnoea or sudden and simultaneous cessation of respiration and cardiac activity. In a further experiment, the authors tried to adjust the exposure in order to keep rats in stage 3. This could not easily be achieved and inadvertent changes to stage 2 or 4 often occurred. After approximately 20 to 45 minutes of exposure, surviving rats were killed and brain sections prepared for histopathological examination. A total of 155 rat brains, including 45 rats that had died or been killed *in extremis* within 24 hours after exposure and 110 killed at 24 hours or later, were found to have lesions of the corpus callosum, pyriform cortex and neocortex, corpus striatum, pyriform and neo-cortex, substantia nigra, dienecephalon, ventral hippocampal commissure, and optic nerves, chiasm and tracts; the results are detailed below. Additionally, 71 rats that had died or were killed at all stages during or after exposure had no histopathological brain changes (Levine and Stypulkowski, 1959).

The corpus callosum of rats that died or were killed 2 to 5 hours after exposure revealed fenestration and spaces between fibres. Nuclei of intrafascicular oligodendroglia were shrunken and had darker staining (haematoxilin/eosin or luxol fast blue/cresyl violet or periodic acid). At 24 hours after exposure, the lesions were well demarcated, fibres pale, oligodendroglia in fenestrated and non-fenestrated parts shrunken and pyknotic. Nucleoli of astrocytes were normal or reduced in number. Vessels were congested. At 48 hours after exposure: persistence of pyknotic neuroglia, endothelial hyperplasia, and increased numbers of macrophages were noted at the margins of lesions and around blood vessels. There was less prominent fenestration. One month after exposure: shrunken corpus callosum, demyelination obvious. Increased number and

size of astrocyte nuclei were noted. The distribution of the lesions in the corpus callosum showed a high variability.

In the corpus striatum, frequently vessels were dilated, but not necrotic (except in the severest cases); grey and white matter were necrotic (shrunken, pyknotic, pale, vacuolated). White matter seemed to be more involved, also in less severe lesions. Oligodendroglia nuclei were often pyknotic but the changes were less pronounced than in the corpus callosum. Endothelial hyperplasia was observed at 48 to 72 hours. Some macrophages were observed, but less pronounced than in corpus callosum. Patchy vacuolisation of the grey matter was frequently observed. The anterior portion of the striatum was more frequently involved, also when the lesion was less severe.

The pyriform and neo-cortex excised 2 to 5 hours after exposure displayed cell shrinking (clear perineural spaces, pale staining). At 24 hours, necrosis of neurons and damage of glia cells was observed. A peripheral zone of vacuolisation was reported. Of the hippocampus, most frequently neuronal necrosis of the dorsal pyramidal cell layer was observed in particular in the medial and anterior portion. The substantia nigra had focal neuronal and white matter lesions. The dienecephalon showed symmetrical zones of necrosis in the medial, ventral, and lateral thalamic nuclei. (These were observed only in severely intoxicated animals that died within the first 24 hours after exposure.)

In the anterior commissure, lesions, as in the corpus callosum, appeared in the middle part. Lesions of the ventral hippocampal commissure were, as in the corpus callosum, in the middle part sometimes also extending laterally to the fimbria. Finally, mild vacuolation was observed in the optic nerves, chiasm and tracts of some animals.

The authors reported that of 64 large (200 - 300 gbw) rats surviving for 24 hours, only 11 had no brain lesions, whereas of 108 small (100 - 200 gbw) rats surviving for 24 hours, 51 showed no any brain lesions. In large rats, the corpus callosum was the structure most frequently affected; the corpus striatum was affected only in conjunction with corpus callosum, and the cortex was only infrequently involved. In small rats, the striatum was the most frequently affected brain region; the corpus callosum was only affected in far fewer animals, while necrosis of the cortex was more frequent. Rats that only experienced stage 1 and 2, or less than 10 to 15 minutes of stage 3 symptoms, mostly did not have any brain lesions. Stage 3 intoxication for more than 15 minutes produced lesions in the corpus callosum and basal ganglia, but not in the cortex and only very rarely in the hippocampus. Only a few minutes exposure to stage 4 was sufficient to cause damage to the grey matter of cortex, thalamus, hippocampus, striatum and cerebellum (Levine and Stypulkowski, 1959). The distribution of brain lesions was further investigated in male and female Lewis rats (> 200 gbw) exposed to HCN so that they were unconscious for 20, 30, 45 or 60 minutes. The corpus callosum was most susceptible and the lesions were most

pronounced in the mid-core section decreasing towards the anterior end and the lateral borders. The author concluded that the distribution was closely related to the blood flow to and distribution of blood vessels over this brain area (Levine, 1969).

In another study, albino rats (2/group, 250 gbw; not further specified) were exposed to HCN vapours until they reached stage 3 for 30 minutes. The animals were perfused at 1, 2 and 24 hours after exposure with glutaraldehyde-phosphate buffer (pH 7.4) and the brain dissected and examined by light and electron microscopy. Single rats were examined after 1 and 3 weeks. Two other rats received a continuous *i.v.* infusion of cyanide keeping them in stage 3 for 20 minutes and were perfused with glutaraldehyde/phosphate buffer (pH 7.4) during the infusion of cyanide. Brain abnormalities were restricted to the core of the corpus callosum. In rats fixed during cyanide exposure, no light microscopic changes were observed. Electron microscopy revealed mild to moderate distension of a few myelinated and unmyelinated fibres, amorphous debris, occasional dilated vesicles and swollen mitochondria in the core of the corpus callosum. One hour after HCN exposure, a faint pallor of the corpus callosum was observed by light microscopy. Electron microscopy showed the same but more extended and more severe lesions as described above. After 2 hours, the core of the corpus callosum appeared fenestrated using light microscopy. Electron microscopy revealed distended axons of the core of the corpus with some spaces filled with debris. Myelin lamellae were intact. Oligodendrocytes and astrocytes appeared normal. In the centre of the lesion, in the posterior part, the beginning of necrosis was observed with empty and swollen axons, vacuolation and disintegration of glial cells. At 24 hours after exposure, the lesions were more severe and more widely distributed. Some axons accumulated dense bodies, mitochondria, vesicles and microtubules. Glia cells showed irregular nuclear shape, swelling of the cytoplasm, increase of engulfed material and glycogen granules. Occasionally, migration of leukocytes in the vicinity of the vessels was observed. At 1 and 2 weeks after exposure, the extent of the fenestrated zone in the corpus callosum was decreased, but empty myelinated axons were still observed. Many myelinated and unmyelinated axons contained dense bodies, mitochondria, microtubules and vesicles. Phagocytic cells had engulfed myelinated fibres (Hirano *et al*, 1967). The regenerative process was followed up in another experiment using the same exposure pattern. Brains were dissected at 1 week to 6 months after exposure. Observations included differentiation and re-myelinisation of axons at different stages indicating repair and reconstitution of damaged brain areas over a period of several months (Hirano *et al*, 1968).

To study the effects of cyanide on the optic nerve, adult male Charles River rats received *s.c.* injections of NaCN every 2 or 3 days (not on weekends) for 3 months. A first group received initial doses of 4 mg/kgbw, which was increased by 0.2 mg/animal at each dosing to a maximum dose of 14.8 mg/kgbw (non-lethal as determined in a prior experiment). In another group, initial doses of 8 mg/kgbw were increased by 0.4 mg/animal/dosing to a maximum non-lethal dose of 11.7 mg/kgbw. Untreated controls (number not specified) were included in both experiments. In the first experiment, 72 of 104 rats died, 42 in the first 3 weeks, in the second experiment 77 of

92 rats died, 65 in the first 3 weeks. At various time intervals, rats were killed and brain optic nerves and eyes further examined microscopically. Several animals that died during the study were reportedly blind before death occurred. Optic nerves of severely affected rats showed focal constriction in a small anterior retrobulbal zone; 20% of the experimental rats showed these lesions. Microscopic examination revealed axial pallor of the myelin staining, diffuse vacuolation of nerve bundles and, in some animals, glial proliferation and pyknosis. Some animals showed severe focal necrosis of the optic nerve and extensive invasion by neuroglia. The damaged zone was usually less than 3 mm. Changes in the optic nerves were always accompanied by changes in the corpus callosum. Some of the mild changes observed were also observed in controls and could be attributed to the experimental procedure. Examination of the eyes showed no substance-related changes. In particular, no changes in the distal portions of the nerves were observed. Most of the rats had lesions in the core part of the corpus callosum of the brain. No clear correlation could be derived with regard to the length of the dosing period. No pathological findings were observed in rats receiving a total cumulative dose of 18.3 mg/kgbw or less or a single dose of 6.9 mg/kgbw or less (Lessel, 1971).

Brierley *et al* (1976) attempted to separate specific cyanide effects on the brain from those induced by hypoxia by infusing NaCN solutions at a rate (0.0903 mg/min) that would not immediately induce apnoea in 3 groups of anaesthetised Wistar rats (8 to 11 male and females, 220 - 500 gbw). Respiration, electro-cardiogram (ECG) and electro-encephalogram (EEG) were recorded. Group 1 (8 rats) was infused until apnoea occurred, after 20 to 39 minutes in small rats (220 - 290 gbw) and 81 minutes in big rats (450 gbw). Group 2 (11 rats, 400 - 500 gbw) was treated in the same manner as group 1, but infusion times were 50 to 104 minutes. Additionally, an electro-myelogram (EMG) was performed and blood pressure recorded. Blood samples were taken intermittently and oxygen, carbon dioxide tension and pH were determined. Animals of group 3 (8 rats) were restrained but otherwise treated as group 2, while infusion times were 71 to 116 minutes. Brains of animals in group 2 and 3 were fixed at the end of the experiment and examined microscopically. In group 1, individual respiration and cardiac rates were quite variable in the beginning (raised in 3, decreased in 2 animals). Apnoea occurred after 20 to 39 minutes in all animals and cardiac arrest 3 to 32 minutes later. The EEG showed an epileptic spike wave activity 8 to 28 minutes after the start of infusion. In group 2, 7 of 11 animals had several instances of EEG reduction to near isoelectric state with epileptic spikes before that reduction. EEG showed evidence of recovery 10 to 15 minutes after termination of the infusion. Respiratory rate and depth increased in most of the animals. Brief apnoea occurred in 3 animals. Partial oxygen pressure in blood was elevated in treated rats and carbon dioxide tension was decreased compared to controls. Blood pH was elevated initially in exposed animals compared to controls (15 to 73 min) and then fell again, in 3 animals below control values. EMG showed tetanus in all 11 animals for periods of 10 to 65 minutes. Mean arterial blood pressure fell to 30% to 84% of controls after 15 to 50 minutes and then mostly returned to normal and only rose when epileptic seizures occurred. Heart rate was elevated in 9 animals in parallel with the hypotension and

remained variable thereafter. In group 3, 4 animals died from cardio-respiratory failure. Respiratory rates rose in all animals and tetanus and myoclonus occurred in all animals 15 to 30 minutes after the start of the infusion. Heart rates were initially elevated and decreased before the end of the infusions and varied widely thereafter. Brain histopathology revealed slight to moderate brain swelling in 7 group 2 animals and 1 group 3 animal. Microscopic changes were seen in 4 group 2 and 2 group 3 animals and included white matter damage in thalamus and corpus striatum with spongy appearance, dilated perineural and perivascular spaces, neurons with shrunken dark stained nuclei, but no changes in astrocytes, microglia or blood vessels. The authors concluded that most of the changes observed are likely to be indicative of a secondary effect of anoxic damage rather than a direct histotoxic action. However, as a level that did not lead to hypoxic effects could not be reached in the experiment, no firm conclusions on the nature and sequence of effects can be drawn.

Rhesus monkeys (*Macaca mulatta*) (11 animals, 4.65 - 10.5 kgbw) were infused *i.v.* with NaCN solution under light anaesthesia for 2 to 4 hours. Infusion rates varied from 5 to 15 mg NaCN/kgbw/min during the experiments. The total dose was 13 to 36 mg NaCN/animal and the total infusion time varied between 31 and 123 minutes. EEG, ECG, respiratory rate, blood pressure, cerebral venous sinus pressure, end-tidal CO_2 partial pressure in blood and body temperature were recorded. Blood gases, pH, glucose, lactate and pyruvate were determined in arterial and venous blood samples. Neuropathological examination of the brain was performed in 8 monkeys killed at 2.5 to 98 hours; the other 3 animals died during the infusion period (2 - 4 h). Initially, respiratory rate and depth, and heart rates increased in all animals between 2 to 20 minutes after the onset of infusion; in 6 animals they were still elevated after 170 to 225 minutes. Episodes of apnoea occurred in 5 animals and mechanical ventilation was applied. Arterial oxygen tension rose and carbon dioxide partial pressure lowered in all animals initially. Peaks in oxygen partial pressure were obtained 10 to 90 minutes after the onset of infusion. Blood pH initially rose to 7.51 to 7.75 (10 to 80 min after onset of infusion) and then fell to 6.9 to 7.5 (at 46 to 127 min). Blood lactate and pyruvate levels at the end of the exposures showed no clearly treatment-related change. Tetanus, beginning in the finger and toes and spreading to the proximal limb muscles, was observed at 10 to 70 minutes in all animals. No myoclonus or epileptic seizures were observed. Arterial glucose levels did not show a consistent change in the exposed animals. In 10 animals blood pressure fell between 10 and 55 minutes after onset of infusion. After some recovery a continuous decrease in arterial blood pressure was observed in animals that died subsequently. EEG changes included no slow wave response during initial hyperventilation; overall activity was decreased later on. Reduction to isoelectric state occurred only after a major fall in heart rate, respiratory rate and blood pressure. In 7 surviving animals, EEG levels returned to normal after cessation of exposure. Neuropathological examination of the brain of 8 animals only showed ischemic cell changes in the striatum and thalamus of one animal that died during the infusion. No treatment-related brain lesions were observed in the other 7 animals (Brierley *et al*, 1977).

Anaesthetised cats (males and females, 11, 4, 1 and 5/group) were infused *i.v.* with NaCN dissolved in physiological saline at different doses and durations. In group 1 (11 cats), the total dose varied from 9.1 to 20 mg NaCN/animal and infusion times ranged from 75 to 195 minutes; group 2 (4 cats) received 5.7 to 12 mg/animal for 120 to 195 minutes; group 3 (1 cat), 16 mg/animal for 105 minutes, and group 4 (5 cats), 11.5 to 15 mg/animal for 210 to 435 minutes. Aortic and venous blood pressure, blood gases, pH and haemoglobin were measured. EEG records were taken and blood flow of the left common carotid artery was measured. Artificial respiration was applied when apnoea occurred. In group 1, cyanide was infused until the blood pressure fell below 100 mm Hg. In group 2, cyanide infusion was performed until the same degree of acidosis as in group 1 was obtained. The blood pressure was artificially lowered below 100 mm Hg by applying a ganglion blocking agent (hexamethonium bromide) and/or blood depletion. Group 3 was treated as group 1 but with an interruption of artificial respiration of 5 minutes. Group 4 received cyanide infusion until the level of acidosis was similar to group 1 and 2 without significant hypotension.

Most of the cats remained unconscious or died at the end of the experiment. Some recovered but remained lethargic. The cats were killed 6 hours to 5 days after infusion and brains examined histopathologically. During the infusion, carotid blood flow and local blood flows to grey and white matter first increased and then decreased when blood pressure was reduced. The increase was more pronounced in grey matter than in white matter. Development of acidosis and bradycardia was followed by decreased blood pressure. Oxygen partial pressure increased and carbon dioxide partial pressure decreased during the infusion. Acidosis, decreased heart rate and elevation of venous pressure developed in all animals in a comparable manner. Microscopic evaluation of the brain revealed lesions in the deep cerebral white matter in many cats of group 1 with the highest severity in the occipital lobe. The corpus callosum showed lesions in almost all cats, mostly in the posterior portion. The crus of the fornix was also damaged similarly. Pallidum (in particular, anterior and upper portions and internal capsule) and substantia nigra were also frequently affected with varying degrees of damage. In some cats, the anterior commissure was damaged in the central portion, but the optical tract was rarely affected. Cerebral cortex and hippocampus showed no significant lesions except in one animal that died of progressive heart failure. In other cats, the cerebellar cortex showed loss of Purkinje cells. The nature of the changes was fenestration up to coagulation necrosis in the white matter, beaded myelin sheaths, and swollen and destroyed axis cylinders. Glia cells showed shrunken nuclei hyperchromasia and irregular fragmentation of nuclei. Endothelia of small vessels were swollen. Animals of group 2 had similar lesions as group 1, but less severe. In group 4, the corpus callosum was almost free of changes except in 2 animals; otherwise changes were less but comparable to those of group 1. The authors attributed the distribution of the lesions in the brain mainly to the blood flow distribution. They correlated the severity of white matter lesions to the intensity of hypoxia and hypotension during cyanide infusion, but not to the extent of acidosis, total dose of cyanide or

duration of infusion *per se*. It was not possible to explain the palladial necrosis with this hypothesis (Funata *et al*, 1984).

E.2 Influence of cyanide on oxidative metabolism

As early as 1946 the involvement of cytochrome *c* oxidase inhibition in cyanide toxicity was described by Albaum *et al* (1946). After administration of lethal doses of NaCN (5 mg/kg *i.p.*) to adult male rats (no details given) brains obtained immediately after the death of the animals were analysed and compared to those of untreated controls prepared in the same manner. A decrease of cytochrome *c* activity of about 50% was observed in treated animals compared to controls. Additionally, in brain extracts of treated rats, increases of lactic acid, hexose diphosphate, phosphoglycerate, phosphopyruvate, ADP and inorganic phosphate levels and decreases of glycogen levels, ATP and phosphocreatinine were observed.

The effects of cyanide on brain mitochondrial cytochrome *c* oxidase in mice were compared *in vivo* and *in vitro*. For the *in vivo* experiments, CD-1 mice (5 males/group) were injected *s.c.* with KCN dissolved in water at a non-lethal (4 mg/kgbw) or lethal dose (20 mg/kgbw) and killed 3 to 5 minutes after injection. Purified brain mitochondria were isolated and cytochrome *c* oxidase levels and mitochondrial respiratory function determined. Vehicle controls were treated in the same manner. A 47% inhibition of cytochrome *c* oxidase was observed at 4 mg KCN/kgbw and a 60% inhibition at 20 mg/kgbw. Mitochondrial respiratory function revealed a 27% and 30% reduction of respiration states 3 and 4, respectively, following 20 mg/kgbw and a non-statistically significant inhibition of 10 and 15%, respectively, at 4 mg/kgbw. *In vitro* studies were conducted in isolated brain mitochondria incubated in 1 to 10,000 µmol KCN/l. At concentrations of 1 to 100 µmol/l, cytochrome *c* oxidase inhibition was linearly dependent on log KCN concentration with an inhibition concentration that caused a 50% reduction (IC_{50}) of 80 µmol/l. Only limited extra inhibition was observed at 100 to 10,000 µmol/l. The respiratory activity of brain mitochondria was biphasically inhibited. Cyanide concentrations of 1 to 100 µmol/l produced a linear inhibition of ADP stimulated respiration of 10 to 25%. When the concentration was raised to 1,000 µmol/l, 80% inhibition of respiration state 3 resulted, accompanied by a small increase in state 4 respiration. The authors concluded that, as they did not see a marked inhibition of respiratory activity at lower than 50% inhibition of cytochrome *c* oxidase, a large portion of the cytochrome *c* oxidase activity could be regarded as a functional reserve (Pettersen and Cohen, 1993).

To study the influence of sublethal acute cyanide doses on the glucose metabolism, groups of 8 to 10 male Swiss-Webster mice were treated with *i.p.* injections of 100 mg of ^{14}C-1, ^{14}C-2, ^{14}C-3(4) or ^{14}C-6 labelled glucose (0.98 to 1.24 µCi), 10 mg of ^{14}C-gluconate-l or ^{14}C-glucuronate-6 (0.84 or 1.12 µCi), alone (controls) or in combination with 5 mg/kg KCN. The exhalation of $^{14}CO_2$ was

followed over a period of 360 minutes. KCN treatment led to a significantly reduced recovery of $^{14}CO_2$ from glucose labelled at C-2, C-6 and (most pronounced) C-3(4) and from glucuronate-6. KCN treatment increased recovery of $^{14}CO_2$ from gluconate-1. According to the authors, the control mice utilised 3 pathways for glucose oxidation, the Emben-Meyerhof-Parnas pathway and tricarbonic acid cycle (EMP-TCA) (aerobic), the pentose-phosphate cycle (anaerobic) and the glucuronic acid pathway. While the latter appeared minor pathways, the EMP-TCA cycle accounted for approximately 57% of the metabolism. The marked decrease in C-3(4) and C-2 labelled glucose utilisation was indicative of an inhibition of the EMP-TCA cycle by cyanide. $^{14}CO_2$ yields from C-1 labelled glucose did not change significantly after cyanide treatment. This suggested that glucose was utilised by an activation of one of the other pathways. Glucuronate-6 conversion was also decreased after treatment with KCN, while $^{14}CO_2$ exhalation from ^{14}C-gluconate was increased. Therefore, the authors concluded that sublethal cyanide doses increased the catabolism of glucose by the pentose-phosphate shunt leading to an increased generation of reduction equivalents (NADPH). According to the authors, this might indicate a compensating mechanism of the cells to maintain a balanced redox state and would also be in accordance with a shift of aerobic to anaerobic metabolism resulting in an accumulation of lactate that was described by other authors (Isom *et al*, 1975).

Isom *et al* (1982) studied the kinetics of the inhibition of cytochrome oxidase activity in liver and brain of male Swiss-Webster mice receiving *i.p.* doses of 5 mg KCN/kgbw. The influence of oxygen treatment and oxygen plus antidote treatment was also studied. Within 2 minutes after KCN treatment liver cytochrome oxidase activity was reduced by 75% when compared to untreated controls. Maximum inhibition was observed in air and oxygen-treated (pure oxygen atmosphere) animals 5 minutes after KCN administration. Cytochrome oxidase activities returned to normal 10 minutes earlier in oxygen-exposed mice (20 min compared to 30 min in air). After 60 minutes, an increase in cytochrome oxidase levels compared to non treated controls was observed. Toxic signs observed in the air-exposed group (respiratory stimulation, agitation, coordination disturbance, convulsion) were not observed in the oxygen treated group. The effect of different oxygen concentrations at various doses of cyanides was also studied by the authors. At 4 mg/kgbw of KCN the effect of oxygen treatment was most pronounced. The liver cytochrome oxidase activity increased from 22% to 66% of controls when the atmospheric oxygen concentration was raised from 11 to 95%. The dose of KCN required to produce 50% inhibition of brain cytochrome oxidase was 24 mg/kgbw in air-exposed rats and 55 mg/kgbw in oxygen atmosphere. Rhodanese activity in brain and liver was determined in both air and oxygen-exposed mice receiving sodium nitrite (100 mg/kgbw *s.c.*) and sodium thiosulphate (1 g/kgbw *i.p.*) at 45 and 15 minutes, respectively, before KCN treatment and 10 minutes after KCN administration (70 mg/kgbw). Control rhodanese activity in liver was approximately 15 times higher than in the brains in both air and oxygen-exposed mice. In animals pretreated with the antidotes, liver cytochrome oxidase levels were not significantly different from controls although the animals had died, but brain cytochrome oxidase was inhibited. In animals receiving a lethal

dose of KCN (10 mg/kgbw) without antidote, cytochrome oxidase, both in liver and brain was inhibited.

To study the effects of KCN on the energy metabolism of rat brain, anaesthetised, tracheoectomised and artificially ventilated Wistar rats (6 - 10 males/group) were infused in the right common carotid and femoral arteries with 2.5 mg KCN/kgbw; blood pressure was recorded through the same cannula. When the animals were in respiratory steady state, 2.5 mg/kgbw in physiological saline was infused for 2 minutes. Arterial blood samples were taken and after 0.25, 0.5, and 1 hour the brain was frozen (by pouring liquid nitrogen into a plastic funnel fitted to the exposed skull) and stored in liquid nitrogen for further analysis. Controls (16 animals) prepared in the same manner received intracarotid infusion of physiological saline only. In recovery animals, the infusion wound was closed and they were followed for 3 to 168 hours. Thereafter, surviving animals (4 animals died beforehand) were again surgically prepared for brain freezing. For histopathological analysis, brains were infused with formaldehyde/glacial acetic acid. The dose used in this study produced acute suppression of conscious behaviour and abolition of EEG activity in all animals. The EEG remained depressed for up to 3 hours followed by a gradual return of slow waves by 6 to 24 hours and return to normal after 7 days. Blood analysis resulted in a moderate metabolic acidosis in animals treated with KCN that returned to normal within 1 hour after administration. Mean arterial blood pressure, oxygen and carbon dioxide partial pressure were not different from controls. Body temperature was unchanged in treated animals compared to controls. KCN treatment produced an increase in blood and cerebrospinal fluid pyruvate and lactate levels that reached a maximum at 15 minutes and returned to control levels at 1 to 3 hours. Tissue lactate and pyruvate content remained elevated up to 6 hours after administration. Brain ATP decreased and ADP and AMP increased greatly within 15 minutes. ADP and AMP returned to normal after 3 hours whereas ATP was continuously decreased for up to 24 hours. Near total depletion of brain glycogen levels were observed in the KCN treated groups at 15 minutes with a gradual restitution during the following 3 to 6 hours. Tissue glucose was maintained at or above control levels for 15 minutes to 3 hours. Brain cytochrome *c* oxidase levels were reduced by 52% at 15 minutes in the KCN treated animals compared to controls. Histopathological examination of the brain showed no clearly treatment-related changes in KCN treated animals. The authors concluded that an injection of 2.5 mg/kgbw produced a completely reversible effect on brain metabolism without detectable damage, while a higher dose level as shown in pre-experiments was immediately lethal (MacMillan, 1989).

The effect of cyanide treatment of PC12 cell cultures on ATP, ADP and AMP levels was studied by measuring cellular levels of the adenylphosphates by HPLC analysis and UV-detection 2.5 to 30 minutes after incubation with 10 mmol KCN/l. ATP levels were significantly reduced to 50 to 70% of control levels at all time points, while ADP and AMP levels were not altered significantly. Pre-incubation with diltiazem 0.01 mmol/l for 15 minutes before KCN was added and incubated for 30 minutes did not alter the depletion of ATP (Maduh *et al*, 1991). The

reduction in ATP levels at 2.5 minutes occurs sooner than the calcium influx reported by Johnson *et al* (1987b) and parallels alterations in cytosolic pH reported by Maduh *et al* (1990a) (Appendix E.3).

Changes in brain metabolism were evaluated by ^{31}P-NMR spectroscopy of adult Sprague-Dawley rats (3/group, sex not stated), with implanted surface coils in their heads, after single *i.p.* injection of 3, 4, or 5 mg KCN/kgbw. One animal received 6 mg KCN/kgbw. ^{31}P-spectra were recorded prior to cyanide administration and every 150 seconds over 90 minutes after administration of KCN. All doses caused the same type of NMR changes and differences were only observed in the duration and intensity of the effects. Within the first 150 seconds after injection phosphocreatinine levels decreased, inorganic phosphate increased and the tissue pH decreased (to 6.7 at 6 mg/kgbw). Sugar phosphate and glycerophosphate peaks were not significantly altered and ATP was only decreased at 6 mg KCN/kgbw (≈ 30 to 40% of control levels), but not at the lower dose levels (Decorps *et al*, 1984).

E.3 Changes in cytosolic calcium-levels and cytosolic pH following cyanide treatment

The involvement of intracellular calcium release was studied in an *in vitro* experiment using PC12 cells, a transformed cell line (the primary cell being a neurosecretory cell from rat phaeochromocytoma tumours) that was used as a neuronal model (Johnson *et al*, 1987b) Concentrations of 0.1 to 10 mmol KCN/l were added to the cell system that was loaded with a fluorescence indicator (Quin II) to detect the change in intracellular Ca^{2+}-levels. A dose-dependent rise in cytosolic calcium levels was observed within 15 to 30 minutes after addition of KCN. Cell viability was assessed using the trypan blue exclusion assay. Only concentrations of 10 mmol KCN/l produced a significant reduction in viable cells within 30 minutes compared to pretreatment control values.

Compared to the KCN treatment, 50 mmol KCl/l produced a more rapid rise in cytosolic calcium levels (5 min) in the same cell system due to activation of voltage dependent calcium channels and the accumulation after 15 and 30 minutes was much less than with KCN indicating that the KCN effect is not due to potassium ions alone. In cells depolarised before with KCl, KCN produced a larger increase in cytosolic Ca^{2+} than with either KCl or KCN alone. Diltiazem pretreatment blocked both KCl and KCN-mediated increase in cytosolic calcium levels. In a second experiment it was demonstrated that, in low calcium medium, the increase in cytosolic calcium levels induced by cyanide was not due to the mobilisation of intracellular calcium. According to the authors, the cytosolic accumulation of calcium observed in this experiment may be a secondary effect from decreased activity of Ca-ATPase and Ca-Mg-ATPase. The gradual increase is typical of a metabolic inhibition while direct activation of receptor or voltage activated channels would result in a sudden rise in cytosolic calcium levels.

In a follow up experiment, PC12 cells were incubated with 0.01 to 10 mmol KCN/l for 30, 60 or 120 minutes and examined by transmission electron microscopy and scanning electron microscopy. Cytotoxicity was assessed by measurement of lactate dehydrogenase release and trypan blue exclusion assay. Incubation with 1 to 10 mmol KCN/l for 1 to 2 hours resulted in depletion of secretory granules (neurotransmitter granules of noradrenaline and dopamine), alignment of remaining granules along the plasma membrane and mitochondrial swelling (most prominent effect). Addition of diltiazem (0.01 to 0.001 mmol/l) to the incubation medium 15 minutes prior to KCN prevented all these effects. With scanning electron microscopy, the loss of microvilli and blebbing of the plasma membrane were also observed. These symptoms were reduced, but not completely inhibited by prior treatment with 0.01 mmol diltiazem/l. Treatment of the cells with 10 mmol KCN/l led to an increased lactate dehydrogenase release after 60 minutes that was attenuated by diltiazem pretreatment. Cell viability was reduced by 54% after 60 minutes of incubation with 10 mmol KCN/l, but this did not occur after diltiazem pretreatment. However, at 120 minutes, cell death was also observed in cells treated with the calcium antagonist. This experiment confirmed the finding that an increase of cytosolic calcium through enhanced Ca^{2+} influx contributes to the cellular damage induced by cyanide and could also be responsible for the increased release of neurotransmitters from storage granules in neuronal cells (Maduh *et al*, 1990a).

Maduh *et al* (1990a,b) studied the effects of KCN on intracellular pH using 2',7-bis(carboxyethyl)-5(6)-carboxyfluorescein loaded rat phaeochromocytoma P12 cells. The fluorescein is trapped in the cells and can be used as an indicator of cytosolic pH. At concentrations of 1 and 10 mmol KCN, but not at 0.1 mmol, intracellular pH was rapidly and significantly decreased in a concentration dependent manner. 10 mmol KCl did not influence the cytosolic pH indicating that the effect was cyanide rather than K^+ driven. Lowering the pH of the incubation medium enhanced the effect of cyanide while a rise in external pH attenuated the effect. Removal of Ca^{2+} from the incubation medium or adding the calcium channel blocker diltiazem (0.01 mmol/l) delayed the onset and reduced the magnitude of the cyanide-induced drop in intracellular pH. Removal of sodium ions from the medium enhanced the effect, reintroduction of Li^+ or Na^+ reversed it, suggesting an involvement of the Na^+/H^+ exchange mechanism. Pretreatment of the cells with amilorid (0.2 mmol/l) (an inhibitor of the plasma membrane Na^+/H^+-antiporter which works by binding on the outer plasma site of the transporter) diminished the cyanide effect, as it seems to block the same antiport system. However, amilorid also inactivates Na^+/Ca^{2+}-exchange systems which could, according to the authors, also alter the response to cyanide. While cyanide was blocking the Na^+/H^+-antiport system, it was still able to increase its response to extracellular pH. Cytoplasmic acidification also disrupts Ca^{2+} transport processes by the interaction of hydrogen ions with voltage-dependent calcium channels. Thus cyanide effects on intracellular calcium levels may, in part, also be triggered by its intracellular acidifying effect.

Yang *et al* (1996) studied the interaction of KCN with the IP_3 Ca^{2+} signalling system in P12 cells. KCN concentrations of 1 to 100 µmol/l induced a rapid rise in IP_3-levels that reached its maximum after 60 minutes. A phospholipase C inhibitor (U73122) blocked the response indicating that it was mediated by phospholipase C. Removal of Ca^{2+} from the incubation medium, chelation of intracellular Ca^{2+} and treatment of the cells with Ca channel blockers (nifedipine or $LaCl_3$) partially inhibited the response, indicating its partial dependence on calcium.

Brain calcium levels were determined *in vivo* in male Swiss Webster mice at different times after *s.c.* administration of KCN. A dose of 10 mg KCN/kgbw produced a significant decrease of whole-brain total calcium at 5 minutes after administration of cyanide. This was followed by a significant increase after 15 minutes and a maximum level of 140 to 145% at 30 minutes after administration. Elevation of the calcium levels persisted for 3 hours and levels returned to normal after 12 hours. Doses of 0.5 to 7 mg KCN/kgbw did not alter brain calcium levels. Injection with diltiazem (600 µg/kgbw *i.v.*) before KCN (10 - 12 mg/kgbw *s.c.*) significantly decreased, KCN-induced rise in whole brain Ca-levels at 15 and 30 minutes after administration. Control calcium levels were not influenced by diltiazem pretreatment. At the dose levels of KCN producing elevated Ca brain levels, tremors were observed in the animals. Diltiazem pretreatment reduced peak frequency and incidence of KCN-induced tremors (Johnson *et al*, 1986).

The effect of NaCN on skeletal muscle contractility *in vitro* was studied in a preparation of rat diaphragm muscle. Contractions of the muscle preparation were stimulated by rectangular currents of 3 milliseconds duration. Directly elicited muscle action potentials were recorded from surface fibres. At termination of the experiments the muscle preparations were frozen, powdered and dissolved in perchloric acid. After centrifugation, the supernatants were assayed for ATP and creatinine phosphate. At 1 mmol NaCN/l there was an increase in twitch tension at a stimulation frequency of 0.1 Hz within 30 seconds of exposure. This attained a maximum 4 minutes later and then declining gradually to 47% of control values for the rest of the recording period. Washout with Tyrode solution resulted in a rapid but incomplete recovery of tension. Baseline tension was not altered by NaCN treatment. At a stimulation frequency of 1 Hz the initial increase of twitch tension was less pronounced and of shorter duration while depression occurred more rapidly and was more pronounced (reduction to 6% of controls). At 0.1 Hz the IC_{50} of NaCN was 0.76 mmol/l and at 1 Hz, 0.14 mmol/l. NaCN produced a marked depression in creatinine phosphate levels (IC_{50} = 0.18 mmol/l), but little or no reduction in ATP levels (not significantly different from controls). NaCN in concentrations up to 1 mmol/l had no effect on resting membrane potential, the passive electrical properties of the membrane or the directly elicited action potential. The amplitude of a contraction induced by high levels of K^+ was reduced by the presence of 1 mmol NaCN/l by 43.9%. The rise and half decay times were also shortened, while the latency period was not changed. To study the effect on the storage and release of Ca^{2+}, the influence of NaCN on caffeine-induced contractions was studied. In the presence of NaCN, the initial phase of

caffeine-induced contractions was statistically significantly reduced, but the amplitude of the second phase was not altered significantly. This suggested that NaCN may impair the storage and release of Ca^{2+} from the sarcoplasmic reticulum or depress the sensitivity of contractile proteins. The latter was considered more likely by the authors (Adler *et al*, 1999).

The effects of NaCN on isolated strips of aorta of rabbit, dog and ferret were studied. In the rabbit aorta, but not in ferret or dog aorta, cyanide concentrations of 10 pmol/l to 10 µmol/l caused small contractions, while concentrations between 10 µmol/l and 1 mmol/l led to relaxation. Cyanide reduced or blocked noradrenaline-induced contractions at concentrations above 10 µmol/l. In dog aorta, cyanide concentrations of up to 10 mmol/l did not block noradrenaline-induced contractions. A similar experiment with ferret aorta was not performed. A concentration of 10 mmol/l alone caused a small contraction in the aorta of each species (Robinson *et al*, 1985a).

The effects of NaCN on smooth muscles of rabbit aorta were further studied by Robinson *et al* (1985b). Strips of isolated rabbit aorta were exposed to noradrenaline to induce contractions. Effects of different compounds on cyanide-induced reduction of contractions were studied by pre-incubation of the strips with those substances before adding NaCN (1 mmol/l) to the incubation medium. Quabain, a K-Na-ATPase inhibitor, and verapamil, a calcium channel blocker, had no influence on the cyanide-induced reduction of the contraction. Cyanide apparently did not interfere in this experiment with K-Na-ATPase or extracellular Ca^{2+}. Cyanide depressed the magnitude of a potassium-induced contraction at high K^+ concentrations, but potentiated the effect at low K^+ concentrations and separated the contraction into two components. The authors proposed that the observed effects could be due to enhancement of vascular smooth muscle permeability to calcium ions by affecting a mechanism involving potassium.

E.4 Cyanide-mediated release of glutamic acid

Mouse brain slices were prepared from cortex, cerebellum and hippocampus of CF-1 mice. Replicates were conducted with slices from different mice. The slices were pre-incubated in buffered medium for 45 minutes and either 2 mmol of KCN/l or 55 mmol of KCl/l. The supernatant was assayed for glutamate with a spectrometric method. After 30 minutes, both treatments produced a comparable increase in glutamate release compared to controls. When calcium was removed from the incubation medium, cyanide did not produce a statistically significant accumulation of glutamate in the medium. The time course of the glutamate release was followed in a second experiment using continuous enzyme linked fluorometry. In a calcium ion-free, as well as a calcium-containing medium, KCN treatment induced a comparable release of glutamic acid within 90 seconds in the slices from the different brain regions. This indicated independence of extracellular calcium. Depolarisation of the slices by 55 mmol KCl/l over

4 minutes produced a calcium-dependent release of glutamic acid (i.e. significant only in Ca^{2+} containing medium). The results indicate that cyanide induces an initial rapid release of glutamic acid that is independent of extracellular calcium ions, while glutamate accumulation over a longer time period (30 min) was only observed when extracellular calcium was available. The initial effect may reflect mobilisation of intracellular calcium by cyanide while the latter effect may represent calcium influx through glutamate gated channels, in particular the N-methyl-D-aspartate (NMDA) receptor channel. High concentrations of glutamate can trigger neuronal degeneration due to excessive calcium influx through NMDA receptor activated channels. It has been shown that NMDA antagonists can block the neuronal damage in experimental models of hypoxia (Patel *et al*, 1991).

E.5 Role of lipid peroxidation for neuronal damage induced by cyanide

Johnson *et al* (1987a) studied lipid peroxidation reactions in mouse brain following cyanide-induced hypoxic anoxia through cytochrome oxidase aa_3 inhibition. Groups of 4 or more male CF-1 mice were injected *s.c.* with KCN (5, 10 or 15 mg/kgbw) with or without pretreatment with diltiazem (600 µg/kgbw *i.v.* 15 min before KCN injection), a calcium-antagonist that blocks voltage-dependent calcium channels, or allopurinol (25 mg/kgbw *i.v.* 15 min before KCN injection), a xanthine oxidase inhibitor. The treatment regimes are given in Table E.1.

Table E.1: Treatment regime and results (Johnson *et al*, 1987a)

Pretreatment	**KCN dose, *s.c.* (mg/kgbw)**	**Time of kill after injection (min)**	**Result (compared to saline treated controls)**
None	5	5, 15, 30, 60	No ↑ in conjugated dienes. No clinical signs
None	5, 10, 15	5 and 60	No ↑ in conjugated dienes. No clinical signs (reversible within 1 h)
None	10, 15	15	Significant ↑ of conjugated dienes. Clinical signs: tremor, seizures
None	10	30	No ↑ in conjugated diene. No clinical signs
None	15	30	Significant ↑ of conjugated dienes. Clinical signs: tremor, seizures
Diltiazem	0	30	Slightly ↓ conjugated dienes
Diltiazem	10, 15	30	Slight ↓ at 10 mg CN^-/kgbw, significant ↓ at 15 mg CN^-/kgbw. Tremors attenuated compared to KCN alone
Allopurinol	0	30	Slightly ↓ conjugated dienes
Allopurinol	10, 15	30	Slight ↓ at 10 mg CN^-/kgbw, significant ↓ at 15 mg CN^-/kgbw. Tremors attenuated compared to KCN alone

At different time intervals after treatment the animals were killed by cervical dislocation, the brains removed, homogenised and extracted with chloroform/methanol. The organic phases were dried, re-dissolved in spectrometric grade cyclohexene and the absorbance between 220 and 250 nm was measured. An increased absorption at 233 nm was considered to be indicative of conjugated diene formation that occurs secondarily to membrane lipid oxidation.

The authors concluded that sublethal doses of cyanide produced a time-dependent, reversible increase in brain lipid peroxidation. Lipid peroxidation may be caused by elevated tissue calcium levels which are consistent with the ameliorating effect of the diltiazem treatment. Elevated cytosolic calcium may activate proteases that, in turn, convert xanthine dehydrogenase to xanthinoxidase. Xanthinoxidase, in the presence of oxygen, catalyses the formation of superoxide radicals that initiate lipid peroxidation. The inhibition of the diene formation by allopurinol treatment indicates that this mechanism may play a role in the cyanide-induced acute central nervous effects.

A similar experiment with comparable results was reported by Ardelt *et al* (1989). In addition to absorption measurements for diene formation, brain oxidant enzyme activities were determined in brain homogenates of mice treated *s.c.* with 7 mg/kgbw of KCN alone or with saline 30 and 60 minutes after treatment. Enzyme activities were measured in aliquots of 10% by weight (per volume) of brain homogenates. Catalase activity was measured using hydrogen peroxide as a substrate and following the reaction with $KMnO_4$ spectrometrically. Glutathione peroxidase was determined by measuring disappearance of NADPH after addition of NADPH, reduced glutathione (GSH) and GSH reductase. GSH reductase activity was measured as NADPH depletion after addition of NADPH and GSH disulphide (GSSG), superoxide dismutase was determined by the nitroblue tetrazolium method and total GSH by the 5,5'-dithio-bis(2-nitrobenzoic acid)-glutathione disulphide (DTNB-GSSG) reductase recycling assay. The administration of 7 mg KCN/kgbw resulted in reduced explorative activity, tremours and occasional tonic seizures with a maximal intensity at 15 to 30 minutes after administration. Complete recovery was observed 45 minutes after administration. Activities of catalase, GSH peroxidase and GSH reductase were significantly reduced compared to controls. The activities of these enzymes returned to control values at 60 minutes after administration. Superoxide dismutase activity was decreased significantly at 60 minutes after administration only. GSH levels were reduced after 30 minutes in parallel with the generation of conjugated dienes while GSSG levels remained unchanged. According to the authors, the inhibitory effect on antioxidant enzymes may contribute to the generation of neuronal membrane peroxidation by cyanide exposure.

The role of lipid peroxidation in cyanide neurotoxicity was evaluated *in vivo* and *in vitro* experiments using mouse brain slices and PC12 cells (see below) by Ardelt *et al* (1994). Groups of 4 male CF-1 mice received single sublethal *s.c.* doses of KCN (7 mg/kgbw) and were killed by

decapitation 15 minutes to 2 hours after administration of the test substance. Brain, liver, heart and kidneys were homogenised and the lipids extracted. Conjugated dienes were measured by UV absorption at 233 nm as an indicator of lipid peroxidation. Elevated levels of conjugated dienes were found in brain and kidney, but not in heart or liver. Additionally, mitochondria and microsomes were obtained from brains of treated mice by differential centrifugation and lipids extracted. Conjugated dienes were also measured in these sub-cellular fractions. No increase was found in the mitochondrial fraction, but in the microsomal fraction a 67% increase of conjugated dienes compared to untreated controls was reported. Brain slices of untreated mice were incubated for 30 minutes with 0.1 mmol of KCN/l in the presence or absence of calcium or presence of calcium and diltiazem (0.1 mmol) (4 to 6 measurements for each experiment). Conjugated diene levels were significantly elevated in the presence of KCN and calcium ions, but not in calcium-free medium or diltiazem treated cells. Hydroperoxide formation was measured in PC12 cell cultures using 2',7'-dichlorofluorescein (Appendix E.6). The assay was standardised with H_2O_2. A significant increase in hydroperoxide formation was observed after 5 minutes incubation with 1 mmol KCN/l in a medium containing 2.2 mmol Ca^{2+}/l, but not with 0.25 or 5 mmol of cyanide or when the medium contained only 1 mmol Ca^{2+}/l. According to the authors, the delayed effects of lipid peroxidation could be responsible for brain damage that does not occur immediately after cyanide intoxication, but after several hours or days and which is accompanied by a gradual loss of central functions or a Parkinson-like syndrome.

E.6 Cyanide-induced apoptosis and oxidative stress

Mills *et al* (1996) used differentiated PC12 cells to study cyanide-induced apoptosis and oxidative stress. Rat phaeochromocytoma PC12 cells that are grown in medium containing nerve growth factor are undergoing terminal differentiation and are dependent on nerve growth factor for survival. Such cultures of terminated PC12 cells were incubated in a medium containing nerve growth factor with KCN in concentrations of 0.01 to 0.5 mmol/l. The lowest concentration causing consistent loss of viability was 0.1 mmol KCN/l. Cell viability was studied using the trypan blue assay and lactate dehydrogenase release assay. DNA fragmentation as an indicator of apoptosis was studied using a modified terminal deoxynucleotidyl transferase dUTP (desoxyuracil triphosphate) nick-end labelling (TUNEL) method. The selectivity of this method for apoptotic cells is based on the presence of 3-OH-DNA fragment ends and their concentration within apoptotic cells. Additionally, intracellular DNA was extracted and analysed by electrophoresis to determine DNA fragments. The morphology of the cells was studied by electron microscopy and free radical generation was detected using the 2',7'-dichlorofluorescein method. Cells are loaded with non-fluorescent 2',7'-dichlorofluoresc<u>i</u>n that is oxidised by intracellular ROS to the fluorescent 2',7'-dichlorofluoresc<u>e</u>in. The fluorescence is quantitatively determined by spectrofluorometric analysis (fluorometry).

Treatment of differentiated PC12 cells with 0.1 mmol KCN/l resulted in a significant increase in cell death within 24 hours. No effect on cell viability was seen at the same concentration in undifferentiated PC12 cells where concentrations of 10 mmol KCN/l are required to reduce viability. The results of the different experiments are summarised in Table E.2.

Table E.2: Summary of experiments on mechanism of cell death in differentiated PC12 cells

Treatment in addition to 0.1 mmol KCN/l for 24 h	Endpoint	Results
-	Viability trypan blue and lactate dehydrogenase assay	Significantly ↓ viability (43% cell death, compared to 5 - 10% in untreated controls)
+ Actinomycin D [a] (2 µ/ml)	Viability trypan blue assay	↓ cell death (20%)
+ Aurintricarboxylic acid [b] (0.01 mmol/l)	Viability trypan blue assay	↓ cell death (25%)
-	DNA fragmentation	Pronounced DNA fragmentation in cells and medium (TUNEL assay and extraction), 33% versus 4 - 6% in untreated controls. Apoptotis characterised by electron microscope and chromatin: degradation and localisation at nuclear membranes. Intracellular vacuolisation, membrane blebbing
-	ROS determination	13% ↑ over control
+ Ascorbate [c] (5 mmol/l)	ROS, viability, apoptosis (TUNEL)	↓ of increased fluorescence by 50%. ↓ of cell death and apoptotic cells (TUNEL assay) 22% compared to 33% without ascorbate and 4 - 6% in untreated controls
+ Catalase [d]	ROS, viability, apoptosis (TUNEL)	↓ of increased fluorescence by 50%. ↓ of cell death and apoptotic cells (TUNEL assay), 16% compared to 33% without ascorbate and 4 - 6% in untreated controls

[a] Transcription inhibitor
[b] Ca^{2+}/Mg^{2+}-dependent endonuclease inhibitor
[c] Neutralisation of intracellular ROS
[d] Neutralisation of extracellular ROS

The results showed that differentiated PC12 cells were about 100 fold more sensitive to cyanide exposure than undifferentiated cells. Cell death was demonstrated to be associated with ROS formation and partly prevented by antioxidant treatment. The cell deaths were shown to be transcription dependent, related to endonuclease activation and DNA fragmentation, characteristics that are indicative of apoptosis. Morphological changes were also consistent with apoptosis.

Kanthasamy *et al* (1997) studied the time course of peroxide generation and its localisation in the cells as well as the influence on antioxidant enzyme systems in undifferentiated PC12 cells. ROS formation was studied using the 2',7'-dichlorofluorescein assay. Confocal imaging of the fluorescence was used to investigate the intracellular distribution. Malondialdehyde, as a measure of conjugated diene formation via lipid epoxides, was determined in the cell homogenates. Catalase activity was determined in cell lysates and CuZn superoxide dismutase activity in homogenates.

ROS was increased in a concentration-dependent manner from 1 mmol of KCN/l. Intracellular imaging revealed an increase in ROS after just 1 minute of exposure and high levels were observed after 15 minutes. It was concentrated in the periphery of the cell, not around the nucleus or the cell membrane. This picture is, according to the authors, consistent with that of glutamate-treated cortical neurons. After 30 minutes of exposure, catalase activity was inhibited with an IC_{50} of 55 µmol/l while superoxide dismutase (SOD) inhibition was less pronounced (IC_{50} = 1 mmol/l). Incubation of the cells with a catalase inhibitor, aminotriazole, resulted in a ROS increase that matched the cyanide-induced increase. KCN incubation (5 mmol/l) induced a significant increase in NMDA that was reduced by pretreatment of the cells with phospholipase A_2 (PLA2) inhibitors, mepracine or dibucaine (100 µmol/l, 30 min). Addition of ascorbate to prevent ROS formation resulted in a reduced increase in NMDA and increased cell viability after KCN (5 mmol/l) treatment for 60 minutes. In conclusion, the experiment showed that cyanide-induced ROS in the periphery of PC12 cells within one minute. The process involves activation of PLA2 and inhibition of catalase. As peroxides accumulate mainly in the cytoplasm between nucleus and plasma membrane, the endoplasmic reticulum may be the major target of lipid peroxidation.

Cyanide-induced generation of intracellular oxidant species ROS and nitric oxide (NO) was also studied in cerebellar granule cells. KCN in concentrations between 25 and 200 µmol/l produced a concentration-dependent generation of intracellular oxidant species that was blocked by NMDA receptor antagonists [(+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohept-5,10-imine maleate (MK-801) or 2-amino-5-phosphonovalerate (AP_5 or APV)] or removal of extracellular Ca^{2+} from the incubation medium. Selective inhibition of NO synthetase by N^G-nitro-L-arginine methyl ester (L-NAME) or reduced haemoglobin as well as selective degradation of peroxygen species by catalase or SOD both reduced oxidant-induced fluorescence of 2',7'-dichlorofluorescein by 50%. Additionally, a correlation of NO and ROS levels with NMDA formation as an indication of lipid peroxidation was observed. The authors concluded that cyanide activates NMDA receptors to generate ROS and NO which may lead to further cytotoxic reaction products such as the peroxynitrite anion ($OONO^-$), and lipid peroxidation (Gunasekar *et al*, 1996).

Gunasekar *et al* (1998) studied the mechanism of cyanide-induced increases in reactive oxygen species (ROS) and NO and the involvement of different enzyme systems in cerebellar granule

cells by co-incubation with different enzyme inhibitors. Both NO and ROS generation were monitored using the 2',7'-dichlorofluorescein assay. Reaction with thiobarbituric acid was used as indicator of NMDA and lipid peroxide formation, and lactate dehydrogenase excretion as indicator of cytotoxicity. The results are summarised in Table E.3.

Table E.3: Results of co-incubation experiments of cerebellar granular cells with KCN and different enzyme inhibitors

Inhibitor	**Effects on ROS and NO, compared to CN^- alone** [a]	**Effects on thiobarbituric acid reactive substances; lipid peroxidation products** [b]	**Cytotoxicity (lactate dehydrogenase efflux)** [c]	**Conclusion**
Cheletrine [d] (1 µmol/l)	↓ by 40%	Partial ↓	Partial ↓	PKC involved in ROS and/or NO formation
L-NAME [e] (300 µmol/l)	↓ ≈ 60%	Partial ↓	Partial ↓	NO formation involved
Cheletrine + SOD or catalase (100 U/ml)	Additional ↓ > 50% (no effect of SOD or catalase alone)	Not performed	Not ↓	-
Cheletrine + L-NAME	No additional ↓	Partial ↓, no additional effect	Partial ↓	NO generation regulated by PKC rather than NO synthetase
Quinacrine [f]	↓ by 30%	Partial ↓	Partial ↓	-
Quinacrine + SOD or catalase (100 U/ml)	No further ↓	Not performed	Not performed	-
Quinacrine + L-NAME	Additional ↓ > 60%	Additional significant ↓	Additional significant ↓	Activation of PLA2 plays a primary role in ROS generation, arachidonic acid (product of PLA2 reaction) may play a role in ROS generation
Quinacrine + PKC inhibitors	Additional ↓ 75%	Not performed	Not performed	ROS and NO concurrently produced
Indomethacine [g] (10 µmol)	↓ > 35%	Partial ↓	Partial ↓	Cyclo-oxygenase involved

Table E.3: Results of co-incubation experiments of cerebellar granular cells with KCN and different enzyme inhibitors (cont'd)

Inhibitor	**Effects on ROS and no compared to CN^- alone** [a]	**Effects on TBARS (thiobarbituric acid reactive substances; lipid peroxidation products)** [b]	**Cytotoxicity (Lactate dehydrogenase efflux)** [c]	**Conclusion**
Nordihydroguaiaretic acid [h] (50 µmol)	↓ > 35%	Partial ↓	Partial ↓	Lipoxygenase involved
N-(2-cyclohexyloxy-4-nitrophenyl)-methane sulphonamide [i] (100 µmol/l)	↓ ≈ 35%	Partial ↓	Partial ↓	Cyclo-oxygenase-2 isoenzyme involved
Proadifen [j]	No significant ↓	No significant ↓	No significant ↓	Cytochrome P450 not involved
Indomethacine, nordihydroguaiaretic acid or N-(2-cyclohexyloxy-4-nitrophenyl)-methane sulphonamide [i] + L-NAME	Additional ↓ ≈ 60%	Additional significant ↓	Additional significant ↓	ROS induced by both cyclo-oxygenase-2 and lipoxygenase pathways

[a] Pretreatment 10 min with inhibitors, followed by KCN (100 µmol) 10 min
[b] Co-incubation, KCN (1 mm) in presence of inhibitors for 6 h
[c] Pretreatment with inhibitors 5 min, thereafter addition of KCN (1 mmol) for 36 h
[d] Neutralisation of extracellular ROS
[e] NO synthetase inhibitor
[f] PLA_2 inhibitor
[g] Inhibitor of cyclo-oxygenase, an enzyme metabolising arachidonic acid
[h] Inhibitor of lipoxygenase, enzyme metabolising arachidonic acid
[i] NS398, specific inhibitor of cyclooxygenase 2
[j] SKF525A, specific inhibitor of cytochrome P450

Cyanide-induced generation of NO is mediated by the activation of PKC-regulated NO synthetase in cerebellar granular cells. ROS formation was related to PLA2-mediated production of arachidonic acid followed by its metabolism via the cyclo-oxygenase, in particular cyclo-oxygenase-2 and lipoxygenase pathways. Concurrent inhibition of cyclo-oxygenase/lipoxygenase and NO synthetase also protected against cyanide-induced cell death. The authors postulate that the generation of both ROS and NO can lead to peroxynitrite formation that mediates lipid peroxidation and cytotoxicity.

An *in vivo* experiment was conducted to study differential susceptibility of brain areas to cyanide and reactive oxygen formation. Groups of 3 out-bred male non-Swiss albino mice were injected (2 ×/d) *i.p.* for 1 to 12 days with a sublethal dose of KCN (6 mg/kgbw) that had been shown to induce brain degeneration and motor impairment. Controls were treated with vehicle alone. For antioxidant studies animals were pretreated (2 ×/d) *i.p.* with a spin trapping agent, α-phenyl-*tert*-butyl-nitrone (32 mg/kgbw) for 7 days, prior to initiation of KCN treatment. Further controls included animals treated with α-phenyl-*tert*-butyl-nitrone alone and animals pretreated with vehicle only. Groups of animals were killed on days 1, 2, 3, 6, 9 and 12 of KCN treatment and brains were prepared for biochemical analysis (formaldehyde perfusion, followed by brain removal, immersion in fixative and paraffin embedding). Five to 7 microtome sections of each brain area were prepared. Thionine staining was used to detect necrotic cell death. Brain sections were counter stained with haematoxylin and methyl green for immuno-histochemical analysis using glial acidic fibrillary protein immuno-staining. Terminal deoxynuleotidyl transferase nick-end labelling (TUNEL) staining was used to detect DNA fragmentation using a fluorescence indicator. Labelled DNA fragments in apoptotic neurons emit a bright green fluorescence. Electron microscopy of the brain areas was also performed. In the cortex, widespread DNA fragmentation was observed in KCN-treated animals from day 2 of treatment with a maximum at day 3. This declined again from day 6 to 12 as evidenced by TUNEL assay and electron microscopy. No necrotic or inflammatory changes or glial cell activation could be detected in the cortex. The apoptotic damage was localised predominantly in the parietal and suprarhinal regions of the motor cortex. In the substantia nigra, bilateral necrotic cell death was detected after 1 day of KCN treatment and progressively increased to day 12. The change was characterised by gross vacuolisation. An increase in glial acidic fibrillary protein immuno-staining was observed after 2 days. Extensive bilateral gliosis was seen from day 3. DNA fragmentation was absent in this brain area. Antioxidant (α-phenyl-*tert*-butyl-nitrone) pretreatment resulted in a significant decrease in TUNEL staining in the cortical area indicating a role of ROS in the apoptotic cell death mediated by cyanide in the cortex. In the substantia nigra, pretreatment with α-phenyl-*tert*-butyl-nitrone had no significant effect on KCN-induced cell loss or gliosis, indicating that either ROS play a minor role in cell necrosis mediated by KCN in this brain area or that the inhibition of ROS formation was not high enough to suppress the response (Mills *et al*, 1999).

E.7 Influence of cyanides on neurotransmitter release in neuronal cells

E.7.1 Catecholamines

The extent of catecholamine releases from neuronal model rat PC12 phaeochromocytoma cells and rat brain cortical slices induced by cyanide was studied by Kanthasamy *et al* (1991a). Changes in catechol metabolism were monitored by measuring the levels of the dopamine precursor 3,4-dihydroxyphenylalanine and its degradation product 3,4-dihydroxyphenylacetic acid (DOPAC) in the cell system. A dose and time-dependent increase in dopamine secretion was observed in PC12 cells following incubation with 1 to 10 mmol KCN/l for 5 to 30 minutes. The release reached a maximum of 250% above untreated controls at 10 mmol KCN/l after 30 minutes. Intracellular dopamine was concomitantly depleted. Even low concentrations in the range of 0.25 to 0.5 mmol were reported to cause an increased dopamine release. A concentration of 10 mmol KCl/l did not influence dopamine release indicating that the effects were not related to K^+ ions. KCN-induced dopamine release was blocked in Ca^{2+} free medium or when cells were pretreated with diltiazem (10 µmol/l). Release of [^{3}H] nor-adrenaline from rat cortical brain slices prior loaded with the radioactive neurotransmitter was increased after addition of 10 mmol KCN/l, but when exposed to 10 mmol KCl/l. In a calcium-free medium or after diltiazem pretreatment the release was only partially inhibited.

In vivo experiments were conducted by the same authors to confirm these findings. *In vitro* observations with phaeochromocytoma cells revealed a dose-dependent release of catecholamines following cyanide treatment (Kanthasamy *et al*, 1991b). Male non-Swiss albino mice (3 - 10/group) received single doses of 5 or 10 mg KCN/kgbw *s.c.*, 4 doses of 5 mg/kgbw every 15 minutes or an intra-cerobroventricular injection of 15.6 µg. Two additional groups were either adrenalectomised and then injected with a single dose of 5 mg KCN/kgbw, or pretreated with pargyline followed by 5 mg/kg KCN. Concurrent controls received the same dose regime of saline. Blood samples were collected 5 or 15 minutes after the single doses, or 5 minutes after the last dose in the multiple dose experiment. The treatment regimes are summarised in Table E.4.

Plasma catecholamines were extracted with alumina using 3,4-dihydroxybenzylamine as internal standard, and released from alumina with nitrogen-purged perchloric acid (0.1 mol/l) containing sodium bisulphite (0.1%) as an antioxidant. Standards containing noradrenaline, adrenaline and dopamine were treated in a similar manner with a recovery of 75 to 85% from plasma. The analysis of the extracts for the catecholamine content was performed by HPLC.

Pargyline pretreatment was used to study the possible role of altered de-amination on the catecholamine levels. The substance is known to increase plasma catecholamines due to mobilisation from extra-granular cytoplasmic stores and decreased de-amination.

The results of the different experiments are summarised in Table E.4. As dopamine levels remained unaltered in all experiments compared to the controls, they are not reported in Table E.4. Additionally, the *s.c.* LC_{50} in these animals was reported to be 12 mg KCN/kgbw.

Table E.4: Results of studies by Kanthasamy et al (1991a,b)

Dose regime (KCN), (mg/kgbw *s.c.*)	Noradrenaline	Adrenaline	Symptoms
1 × 5	5 min: 2 × above control 15 min: slight ↑ (not significant)	5 min: 8 × above control 15 min: not significantly different from control	↓ motor activity, tremors after 5 min, recovery after 15 min
1 × 10	5 min: ≈ 2.5 × above control 15 min: ≈ 3.5 × above control	5 min: ≈ 10 × above control 15 min ≈ 26 × above control	No deaths, ↓ motor activity, convulsions persistent for at least 15 min
4 × 5, every 15 min	5 min after last dose: 3 × above controls	5 min after last dose: 12 × above controls	Extreme effects: tremors, convulsions, muscular incoordination
15.6 µg, intracerebroventricular	5 min after injection: no changes	5 min after injection: No changes	Tremors, ↓ motor activity, laboured breathing, convulsions (some animals) all reversible within 1 min after treatment
1 × 5, 1 h after pargyline 100 mg/kg *i.p.*	5 min after KCN dose: slight, but non-significant ↑	5 min after KCN dose: significant ↑, comparable to cyanide alone, no influence of pargyline.	Not reported
1 × 5, 5 d after adrenectomy	Significant ↑ comparable to that of non-adrenectomised mice	No detectable amounts present in adrenectomised controls and KCN treated mice	Not reported

From these experiments the authors concluded that acute cyanide doses produced a rise in plasma catecholamine levels. The mechanistic experiments suggested a release from granular stores rather than interference with de-amination or extra-granular release (no alteration with pargyline pretreatment) and stimulation of adrenal excretion, as adrenectomy blocked the increase in adrenaline. Adrenectomy also resulted in elevated noradrenaline levels. It was concluded that its release originated from sympathetic neurons. The authors postulated that a calcium-dependent process may be involved. They discussed a catecholamine-induced cardiac stimulation that, in combination with the block of the cytochrome oxidase, increases the sensitivity of the heart as

compared to other tissues to cyanide poisoning and could lead to the myocardial damage that was observed in cyanide poisoning (Kanthasamy *et al*, 1991b).

To study the influence of cyanide on neurotransmitter levels, male non-Swiss albino mice (group size not stated) received sublethal doses of KCN (2 × 6 mg KCN/kgbw; 60% of LD_{50}) for 7 days. The animals were killed 16 hours after the last dose and brains removed and dissected into striatum, hippocampus and cortex. In an additional acute experiment, a single dose of 6 mg KCN/kgbw was injected *s.c.* and animals killed 5 minutes later. After the first treatment most mice showed laboured breathing, depression and slight tremors for 5 to 10 minutes after dosing. After 2 to 3 days, tremors, convulsions and muscular incoordination lasted for about 1 hour after dosing. On day 3 to 5, about 30% of the animals had marked behavioural changes for several hours after dosing. Dopamine concentration was significantly decreased in striatum and hippocampus, but not in the cortex of animals repeatedly dosed compared to controls. No changes in dopamine levels were observed in the brains of the animals receiving only a single dose. The behavioural effects could in part be reduced by levodopa treatment (dopamine antagonism). Tyrosine hydroxylase immuno-histopathological staining revealed a reduced number of Tyrosine hydroxylase positive cells in the substantia nigra (pars compacta and pars reticulata) indicating a loss of dopaminergic neurons after repeated cyanide dosing (Kanthasamy *et al*, 1994).

Dopamine, DOPAC and homovallinic acid neurotransmitter levels were measured in brain micro-dialysis fluid of moving Sprague-Dawley rats (males, group size not given) before and during perfusion with 0.2, 1 or 2 mmol NaCN/l solution for 1 hour. No significant change in dopamine levels was observed at 0.2 mmol NaCN/l. At 1 and 2 mmol/l, dopamine levels increased rapidly between 15 and 60 minutes. Maximum levels were observed at 40 minutes and were 25 and 63 fold higher than the basal levels. Within 60 minutes after the start of renewed perfusion with Ringer solution, dopamine levels decreased to normal again. A small decrease in DOPAC and homovallinic acid levels was observed in the 1 and 2 mmol groups from 40 minutes after the start of re-perfusion with Ringer solution reaching the maximum decrease at 60 and 100 minutes after the start of re-perfusion. No histopathological changes were seen in the brains that could be attributed to cyanide treatment or to the surgery 1 and 7 days after the experiment (Kiuchi *et al*, 1992).

The effect of cyanide on the nigrostriatal system in awake, freely moving male Sprague-Dawley rats was studied using a micro-dialysis technique. Extracellular striatal levels of dopamine, DOPAC, homovallinic acid and 5-hydroxyindolacetic acid were measured after *i.p.* injection of NaCN (2 mg/kgbw). Levels of dopamine were significantly elevated in the extracellular fluid 20 to 60 minutes after NaCN injection compared to saline treated controls. Another increase was observed at 100 to 160 min. Levels returned to normal within 180 minutes. A significant decrease of DOPAC (10 - 40%) was observed from 20 minutes until the end of the observation period (180 min). The level of homovallinic acid was significantly increased (142 - 243%) at 40 minutes after

administration, but returned to normal by 100 minutes. The level of 5-hydroxyindolacetic acid was decreased by 60% after 20 minutes and returned to basal level after 120 minutes. The increased levels of extracellular dopamine and homovallinic acid in the striatum of cyanide-treated animals indicated an increased release or another interference with dopaminergic neurons. The exact reason for the release could not be determined from this experiment, according to the authors (Cassel *et al*, 1995).

The influence of NaCN (0.0001 to 1 mmol/l) *in vitro* on brain samples of rat cerebral cortex and pig striatum was studied by incubation of microprims for 30 minutes that were pretreated with [^{3}H]myo-inositol. After cyanide incubation, agonists (noradrenaline, carbachol and dopamine) were added and posphoinositide hydrolysis was determined by measuring the accumulation of inositol phosphates produced by the hydrolysis of pre-labelled inositol phospholipids. NaCN treatment did not influence basal or drug-stimulated breakdown of inositol phospholipids (Cassel *et al*, 1995).

Neurotransmitter levels in different brain regions were measured in male Sprague-Dawley rats (12/group) receiving 5, 10 or 20 mg NaCN/kgbw by *i.p.* administration; controls received *i.p.* injections of normal saline. The animals were killed (by microwave irradiation) 30 to 60 seconds after administration. Levels of dopamine were determined in cerebellum, frontal cortex, hippocampus, olfactory tubercle and striatum. DOPAC levels were determined in frontal cortex, hippocampus, olfactory tubercle and striatum, homovallinic acid levels in hippocampus, olfactory tubercle and striatum. Dopamine levels were decreased statistically significantly in striatum only in a dose-dependent manner from 5 mg/kgbw compared to controls. DOPAC levels were not significantly altered, but in the dopamine-rich brain regions (striatum, olfactory tubercle and hippocampus) the main metabolite of dopamine, homovallinic acid, decreased significantly. A clear dose relationship was only observed in the striatum. At 20 mg/kgbw NaCN statistically significantly increased levodopa levels in the striatum. Levels of γ-aminobutyric acid were decreased in the cerebellum, frontal cortex, striatum and hippocampus, but only at the highest dose level. Glutamic acid was increased in the cerebellum, striatum and hippocampus, while glutamine was increased in the striatum and frontal cortex only. Cyclic guanosine monophosphate was also increased at the high dose in the cerebellum and hippocampus. Concentrations of acetylcholine and choline were not significantly changed in the striatum (Persson *et al*, 1986).

The effect of cyanide on release of adrenal catecholamines following different stimuli was studied in isolated bovine adrenal glands. Pairs of fresh bovine adrenals were perfused with oxygenated 2-amino-2-(hydroxymethyl)propane-1,3-diol (TRIS)-buffered Locke's solution and equilibrated for 45 minutes. They were then perfused with cyanide solution alone or simultaneously with different agonists in the perfusion medium. Either one of the paired glands or the initial value was used as control. Adrenaline and noradrenaline release was measured analytically in aliquots of the perfusates. Additionally, the influence on Ca-secretion was

measured using $^{45}Ca^{2+}$ pretreated glands. Cyanide (1 mmol/l) alone had no significant influence on catecholamine secretion over a 10 minutes period, but it enhanced Ba^{2+}-induced catecholamine 3 fold, while acetylcholine or K^{+}-induced release was increased only by about 50%. The response to continuous stimulation with potassium or acetylcholine increased by about 30% above controls. Cadmium (that is supposed to stimulate catecholamine secretion via the mobilisation of intracellular Ca^{2+}) was also more effective (≈ 25% increase) in the presence of cyanide. Ca^{2+} excretion was not influenced by 1 mmol/l of cyanide in intact adrenals, but when the cortex was removed the efflux of $^{45}Ca^{2+}$ was decreased and the acetylcholine stimulated increase of $^{45}Ca^{2+}$ excretion was also blocked by cyanide (Borowitz *et al*, 1988).

E.7.2 Amino acids

Yamamoto (1989, 1992, 1993) reported on three experiments on the origin of increased brain neutral and aromatic amino acid levels and its relation to brain damage in cyanide-treated mice.

Male ddy mice (6 - 10/group) were injected *s.c.* with a lethal dose of KCN (8 - 20 mg/kgbw). Some mice were co-administered *i.p.* α-ketoglutarate or oxaloacetate (500 mg/kgbw). Blood, brain and liver samples were taken within 15 minutes when the mice lost consciousness and the biochemical assays were performed in organ homogenates after differential centrifugation. α-Ketoglutarate and, to a lesser extent, oxaloacetate antagonised the lethal effects of cyanide and increased the lethal dose (Yamamoto, 1990). Blood ammonia levels in the cyanide-treated mice were 2.5 fold above controls. This increase was blocked by α-ketoglutarate. Mice treated with 5 mg/kgbw of KCN did not lose consciousness and the ammonia blood levels were only 50% higher than controls. Liver arigino-succinase and carbamoyl phosphate synthetase levels that can control blood ammonia levels were not significantly altered in treated animals. ATP content of the liver, but not the brain of treated mice was significantly reduced compared to controls. Neutral and aromatic amino acid levels (leucine, isoleucine, tyrosine and phenylalanine) were significantly increased in the brains of treated mice compared to controls, but this was inhibited by α-ketoglutarate pretreatment. Levels of other amino acids such as taurine, glutamate, or aspartate were not significantly altered by cyanide treatment (Yamamoto, 1989).

In a follow up experiment, male ddy mice (6/group) were injected *s.c.* with 0, 5, 8 or 10 mg KCN/kgbw in saline. Blood, brain and liver samples were taken 5 minutes after treatment and the biochemical assays were performed in organ homogenates after differential centrifugation. Blood ammonia levels were increased by 38%, 152% and 202% at 5, 8 or 10 mg KCN/kgbw, respectively. A dose-dependent increase in blood tyrosine levels was seen in treated groups compared with saline-injected controls. Brain tyrosine levels showed a significant increase in the 8 and 10 mg/kgbw groups. ATP content of the liver was dose-dependently decreased (28, 44 and 50%) and NADH content was increased by 14, 38 and 48%, respectively. Liver tyrosine

aminotransferase activity was inhibited in a concentration-dependent manner (23, 38 and 44% decrease). Glutamate dehydrogenase activity in the liver was not altered by cyanide treatment. The author postulated that cyanide-induced brain damage can be related to increased blood ammonia levels and increased brain tyrosine levels (Yamamoto, 1992).

The findings were corroborated in a follow-up study of the same author in groups of male Wistar rats (6/group) and male ddy mice (6/group) receiving sublethal or lethal doses of KCN either by *s.c.* injection or oral gavage. The author followed the increase of blood ammonia and aromatic amino acid levels and the symptomatology and subsequently treated groups of the same rat strain with the equivalent amount of ammonia and/or phenylalanine. Combined administration of ammonia and phenylalanine led to a similar loss of consciousness as observed in the KCN-treated animals, while administration of either ammonia or phenylalanine alone did not have this effect (Yamamoto, 1993).

E.8 Cyanide-receptor interactions

The effects of different antagonists on cyanide- and glutamate-induced cytotoxicity (as measured by lactate dehydrogenase release) were studied in rat hippocampal cultures prepared from 17 to 18 days foetuses. The antagonists, 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX), a non-NMDA antagonist, and APV, an NMDA antagonist, were added 2 minutes prior to the agonists. The lactate dehydrogenase efflux produced by 2 mmol NaCN/l was blocked by concurrent treatment with 1 mmol APV/l, while 10 µmol CNQX/l did not block the cytotoxicity. Combined exposure to antagonists did not increase the reduction in cyanide toxicity. The lactate dehydrogenase efflux produced by 100 µmol glutamate/l was partially reduced by either 10 µmol CNQX/l or 1 mmol APV/l, while combined exposure to both antagonists offered additional protection. The results indicated that cyanide toxicity to this cell system could be antagonised by an NMDA receptor antagonist, indicating that the NMDA receptor subtype of glutamate was involved in cyanide toxicity. This also indicated that the cytotoxicity of cyanide could not be attributed to glutamate release, but that NMDA receptors were selectively activated. The authors postulated that the effect could be triggered by a relief of the Mg^{2+} block of NMDA receptors following metabolic inhibition by cyanide or that the glutamate release during cyanide exposure in the experiment was lower than that in the glutamate-treated cultures as low µ-molar amounts of glutamate would also selectively activate NMDA receptors (Patel *et al*, 1993).

In a further experiment, the same authors studied the effects of cyanide on NMDA-mediated Ca^{2+}-influx and NMDA-mediated inward current in cultured hippocampal neurons of foetal rats in the presence and absence of extracellular Mg^{2+}. This was to identify if cyanide interaction with NMDA receptors is direct or mediated via relief of the Mg^{2+}-block of the receptor. Radioligand binding of [^{3}H]MK-801 (NMDA receptor antagonist) was measured to determine direct

interactions with the NMDA-receptor complex. Exposure of hippocampal cultures to 50 µmol NMDA in the absence of Mg^{2+} produced an elevation of Ca^{2+} influx. In the presence of 1 mmol Mg^{2+}/l in the extracellular medium the calcium influx was diminished. 1 mmol NaCN produced a Ca^{2+} influx independent of the Mg^{2+} content of the extracellular medium. Combined exposure to 1 mmol NaCN/l and NMDA resulted in an enhanced response to NMDA in the presence of Mg^{2+} only, but in a reduced response in the absence of Mg^{2+}. At 10 mmol NaCN/l, there was a large elevation of Ca^{2+} alone, without enhanced the effects of NMDA, but only in the presence of Mg^{2+}. In voltage clamp experiments in isolated neurons, 1 mmol of extracellular KCN enhanced the amplitude of NMDA-activated current in the presence of Mg^{2+}, whereas in the absence of magnesium ions no significant enhancement of the NMDA activated current was observed. In the presence of 100 µmol glutamate/l and 10 µmol glycine/l, 1 mmol NaCN/l marginally increased [^{3}H]MK-801 binding to rat forebrain membranes, but only in the presence of Mg^{2+}. These experiments suggest that the immediate enhancement of Ca^{2+} influx may be due to an initial reduction of the Mg^{2+}-block of the NMDA receptor which is energy independent, followed by a gradual increase in Ca^{2+} influx resulting from cellular energy depletion (Patel *et al*, 1994).

Other experiments on NMDA receptor interactions of cyanide were conducted in primary cultures of rat cerebellar granule cells loaded with fura-2, a fluorescence indicator. Ca^{2+} influx and patch clamp currents were studied following co-exposure to NMDA and different concentrations of NaCN as well as Mg^{2+}, NMDA-receptor antagonists (APV, MK-801), modulators of the NMDA-receptor (dithiotreitol, pregnenolone sulphate or arachidonate, phorbol-12-myristate-13-acetate) or voltage sensitive calcium channel blockers (nifedipine, diltiazem) (Sun *et al*, 1997). The results from these experiments are summarised in Table E.5.

Table E.5: Experiments of Sun et al (1997) in rat cerebellar granule cells

Exposure	Result (intracellular Ca^{2+})
20 - 100 µmol NaCN/l alone	No influence on Ca^{2+} influx
NaCN (20 - 100 µmol/l) + NMDA	Dose-dependent ↑ of Ca^{2+} influx; ↑amplitude and duration of NMDA evoked currents. ↑ in single channel opening frequency, no effect on unitary conductance or mean channel open time.
K^+-depolarisation	No change in K^+ depolarisation induced Ca^{2+} levels
+ Mg^{2+}, APV [a], MK-801 [b]	NMDA induced Ca^{2+} levels ↓, no further ↑ following CN^- treatment
+ Dithiotreitol, pregnenolone sulphate or arachidonate	↑ of CN^- response
+ Phorbol-12-myristate-13-acetate	No alteration of CN^- response
+ Diltiazem or nifedipine	No effect on NMDA or CN^- response, indicating no involvement of secondary opening of voltage sensitive Ca^{2+} channels
+ Tetrodoxin [c]	No effects on CN^- response, indicating no involvement of Na^+ activated glutamate release

[a] Competitive NMDA receptor antagonist
[b] Non-competitive NMDA receptor antagonist
[c] Blocks Na+ channel activated glutamate release

From this experiment it was concluded that at low doses of cyanide the enhancement of Ca^{2+} influx is primarily mediated by direct interaction with the NMDA receptor and not with the Mg^{2+} blockade as suggested for higher cyanide concentrations by Patel *et al* (1994). Cyanide seems to interact with one or more of the receptor's modulator sites as demonstrated by the influence on the channel opening frequency, which is similar to the action of other modulators of the NMDA receptor and the increase of the effect of other modulators.

Systemic administration of hydromorphone to rats increased brain cyanide levels by 61% after 15 minutes and was blocked by naloxone, an opiate antagonist. The authors demonstrate that cyanide generation is increased in neuronal tissue by µ-opiate receptor agonists and postulate that it may modulate NMDA receptor response. NMDA treatment of cultured neurons activates NMDA-receptor-mediated calcium channels. Addition of hydromorphone or cyanide increased the calcium levels, while both substances alone (without NMDA) did not have an effect on intracellular Ca^{2+} levels. The enhancement in the presence of NMDA was blocked by thiosulphate or methaemoglobin addition. The authors conclude that HCN could be a gaseous neuronal modulator similar to CO or NO. HCN could be an antagonist to NO as they have a number of opposing actions such as vasodilation (NO) versus vasoconstriction (CN^-); guanylcyclase inhibited by CN, stimulated by NO (Borowitz *et al*, 1997).

To study the interaction of cyanide with the NMDA receptor in mature rat cortical neurons *in vitro*, cortical neurons were incubated for several minutes in extracellular recording solution containing 2 mmol KCN/l. Whole cell measurements of NMDA-mediated currents were performed without KCN and at 1-minute intervals during KCN treatment. A rapid small increase in inward leak current was followed by increased amplitude of NMDA-induced responses that was time dependent. The oxidising agent 5,5'-dithiobis(2-nitrobenzoic acid) (0.5 mmol/l) quickly reversed the action of cyanide. KCN alone only elicited responses that were about 8% of those of NMDA alone. In a series of experiments, the authors identified a receptor subunit (NR1/NR2A) as the target site of cyanide. Some of the effects of cyanide may be mediated, according to the authors, by the formation of a thiocyanate adduct with a cysteine residue located in the NR1 part of the receptor (Arden *et al*, 1998).

Neuronal and glial cells often respond to extracellular stimuli through activation of second messengers often followed by an increased expression of immediate early genes (IEGs) including c-fos and c-jun genes. To study the involvement of second messengers after interaction of cyanide with the NMDA receptor, male Sprague-Dawley rats (number of animals not stated, presumably 10/group) were injected *i.p.* with saline, 0.5 or 4 mg KCN/kgbw. Some animals received the NMDA receptor antagonist MK-801 (3 mg/kgbw, *i.p.*) 30 minutes prior to KCN treatment. Rats were killed and brains dissected 0, 30, 60, 120 and 180 minutes after cyanide administration. The cortex, hippocampus, brain stem and cerebellum were separated and homogenised. western blots were performed on the homogenates. Fos levels were slightly increased in the cortex and cerebellum after 0.5 mg KCN/kgbw and almost doubled compared to untreated controls at 4 mg KCN/kgbw. Most prominent changes were observed at 60 minutes after administration. Hippocampus showed a decreased fos content after cyanide treatment. In the brain stem 4 mg/kgbw of KCN only produced a 40% rise in fos levels over controls, but this further increased at 120 minutes. c-Jun levels were not elevated in any of the brain regions. Administration of MK-801 prior to cyanide treatment abolished or greatly reduced the changes in fos levels (Pavlaković *et al*, 1994).

The effect of NaCN on potassium channels after treatment with potassium channel blockers or glucose free medium was studied in triangularis sterni and diaphragm nerve-muscle preparations of adult ICR mice. Cyanide (10 µmol/l) depressed potassium currents with spontaneous transmitter release under glucose free conditions. The effect was antagonised by diazoxide, an ATP sensitive channel opener. The authors concluded that cyanide depresses ATP sensitive potassium currents directly by interaction with the potassium channel (Chao *et al*, 1996).

E.9 Effect of cyanide treatment on protein kinase C translocation in neuronal cells

Rathinavelu *et al* (1994) studied the activation and translocation of protein kinase C (PKC) in rat brain slices prepared from cerebellum, hippocampus and cortex following treatment with 1 to 10 mmol KCN/l. The effects of NMDA receptor antagonists (APV or MK-801) and CNQX, an AMPA/kainate receptor antagonist, were also investigated. Treatment of hippocampal and cerebellar slices with KCN for 60 minutes resulted in concentration-dependent increases in PKC activity in the particulate membrane fraction and a parallel decrease of PKC activity in the cytosol. The cerebellum was the most sensitive area. In cortex slices, membrane associated PKC activity was not altered by cyanide treatment. PKC translocation reached a maximum at 30 minutes after cyanide treatment and remained constant for 60 minutes in hippocampal membranes. NMDA receptor antagonists significantly decreased the cyanide-induced translocation of PKC from cytosol to membranes in hippocampal and cerebellar slices while AMPA/kainate antagonists had no effect. PKC translocation to the plasma membrane resulted in delayed, Ca^{2+}-mediated neuronal death and was one indicator in the cascade of cyanide-induced Ca^{2+}-mediated cell death. The authors pointed to the fact that the prolonged PKC translocation following cyanide incubation was consistent with that induced by exposure to cytotoxic concentrations of glutamate following stimulation of NMDA sensitive glutamate receptors. According to the authors, the results of the experiments indicated a differential sensitivity of different brain areas, but they also mentioned that the results may also be related to the method used to quantify PKC in this study, which used antibodies to specific PKC isoenzymes, which may not be reacting with the iso-form predominantly present in the cortex.

Pavlaković *et al* (1995) studied the effect of cyanide-induced chemical hypoxia on PKC translocation and cell injury in cultured differentiated PC12 cells from rat brains. The cellular distribution of PKC was visualised by the use of an anti-PKC antibody and confocal laser scanning microscope and quantified by western blot analysis. Cytotoxicity was measured by lactate dehydrogenase efflux determination. In control cells, PKC was localised perinuclearly. Exposure to KCN at 100 µmol/l or 1 mmol/l resulted in a doserelated PKC translocation to organelle membranes and plasma membrane within 30 minutes. This effect persisted for more than 120 minutes. The effect was partly blocked by the PKC inhibitor chelerythrine (1 mmol KCN/l increased membrane bound PKC by 210%, while the PKC inhibitor reduced the percentage to 115%). Pretreatment with the calcium channel blocker nifedipine or incubation in Ca^{2+} free medium reduced or prevented PKC translocation as well. KCN treatment also led to a dose-related change in cell morphology and increased lactate dehydrogenase release compared to untreated control cells. The lactate dehydrogenase release was partially blocked by pretreatment with phorbol-12-myristate-13-acetate (100 nM), an NMDA receptor modulator, nifedipine or chelerythrine added 10 minutes prior to cyanide addition to the culture medium.

APPENDIX F: RELATION BETWEEN LC_{50} AND BODY WEIGHT

From Figure 31 (Section 8.1.4) one might read that, in general, the LC_{50} increases with increasing body weight for all species tested. The data of Barcroft (1931) were analysed with the purpose of predicting the mortality response from the HCN concentration, the exposure duration and the body weight of the mammal. This produced the following regression equation:

$$\text{Probit} = b_1 \times \ln C + b_2 \times \ln t - b_3 \times \ln bw - b_0 \quad \text{(Eq. F.1)}$$

Where C = concentration (mg/m^3)

t = time (min)

bw = body weight (g)

Regression coefficients > 0 for $p < 0.005$: $b_0 = 1.631$, $b_1 = 1.133$, $b_2 = 0.413$ and $b_3 = 0.108$

The probit is described by:

$$P = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{Y-5} \exp\left(-\frac{1}{2}u^2\right) du \quad \text{(Eq. F.2)}$$

Where Y = probit

$100 \times P$ = % response

This regression equation shows that with increasing bodyweight, the mortality response decreases. This is quite conceivable, because HCN has to be absorbed into the cells and form a complex with the respiratory enzyme, cytochrome oxidase. Because smaller mammals have a higher oxygen demand per kg bodyweight than larger mammals, smaller mammals will absorb the lethal dose by inhalation much faster than larger mammals. Not withstanding this general rule, dogs and cats seem to be more sensitive, for the following reasons.

From the data of McNamara (1976) it can be derived that the 5-minute LC_{50} in dogs is 283 mg/m^3 and the 65-minute LC_{50} 125 mg/m^3. Assuming a breathing rate of the dog of approximately 20 l/kgbw/h and a lung retention of 50%, 0.26 mg/kgbw is retained after 5 minutes and 1.49 mg/kg after 65 minutes. This is equivalent to a detoxification rate of 1.3 mg CN^-/kgbw/h or 0.021 mg/kgbw/min. This rate is comparable to the earlier estimate of 0.022 mg/kgbw/min for humans. In addition, the breathing rate of a dog is 22 l/kgbw/h, whereas for humans at rest it is approximately 10 l/kgbw/h. Therefore, the dog absorbs twice the amount of cyanide by inhalation than a human being per unit time but has a comparable detoxification rate. This could explain why the dog is more susceptible than man.

It can also be derived from the data of McNamara (1976) that the LC_{50} in cats (5 minutes) is 325 mg/m^3 and the LC_{50} (65 minutes) is 131 mg/m^3. Assuming a breathing rate for the cat of approximately 16 l/kgbw/h and a lung retention of 50%, 0.22 mg/kg is retained 5 minutes and 1.14 mg/kg after 65 minutes. This is equivalent to a detoxification rate of 0.9 mg CN^-/kgbw/h or 0.015 mg/kgbw/min. This rate is lower than the earlier estimated 0.022 mg/kgbw/min for humans. The breathing rate of a cat is 16 l/kgbw/h, whereas for humans at rest it is about 10 l/kgbw/h. So the cat absorbs in the same time 1.6 times more cyanide by inhalation than a human being, while the detoxification rate is lower. This could explain why the cat is also more susceptible than man.

Barcroft (1931 cited by McNamara, 1976) assumed that the sensitivity of humans to HCN was comparable to that of goats and monkeys. Therefore a concentration-time mortality response was derived from his exposure trials of monkeys and goats, as follows.

$$\text{Probit} = b_1 \times \ln C + b_2 \times \ln t - b_0 \quad \text{..... (Eq. F.3)}$$

Where C = concentration (mg/m^3)

t = time (min)

Regression coefficients > 0 for $p < 0.002$: $b_0 = 15.5$, $b_1 = 2.81$ and $b_2 = 1.37$

On the basis of the probit equation F.2, considering goat and monkey as one group of animals representative for humans, the LC_{50} and LC_{01} values presented in Table 42 were estimated (Section 8.1.5). These LC data are considered to be representative for man.

APPENDIX G: EFFECTS OF BOLUS DOSING VERSUS DRINKING WATER

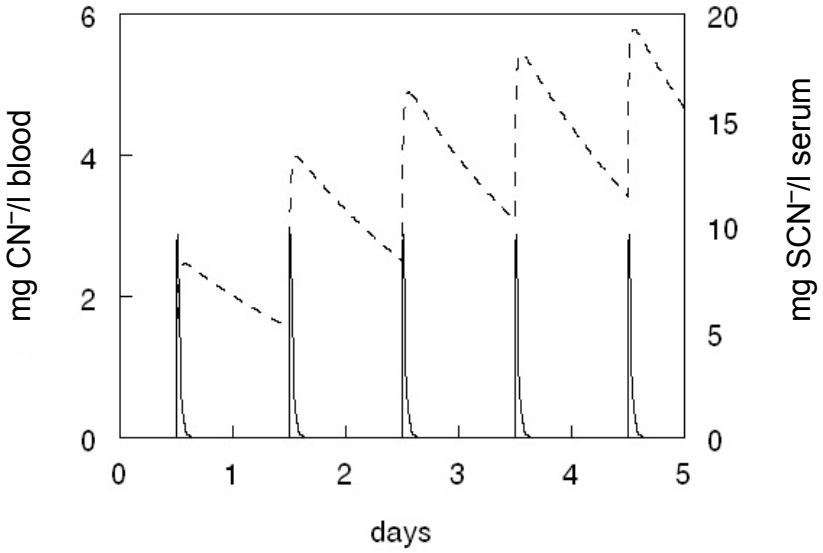
G.1 Blood levels of cyanide in juvenile pigs following dosing as a bolus and via drinking water

Jackson (1988a) claimed behavioural effects in juvenile pigs of a dose of 1.2 mg CN^-/kgbw/d due to an effect on the thyroid. The title of their study suggests dosing via diet, but in fact it was a bolus dose in water given by gavage once a day just before the daily meal of the pigs. In order to compare the real effect on the cyanide level in blood of a bolus dose compared to drinking water uptake distributed over a day, a simulation was carried out on the basis of the following assumptions:

- Cyanide given by gavage is absorbed in 15 minutes
- Cyanide in drinking water is consumed in 10 equal doses spaced over 12 h/d by periods of 72 minutes
- Turnover time of cyanide in juvenile pigs is 30 minutes
- Distribution volume of cyanide is 0.075 l/kg (Schulz, 1984)
- First-pass transformation into thiocyanate by the liver is 75%
- Cyanide is converted by 80% into thiocyanate
- Turnover time of thiocyanate is 2 days
- Distribution volume of thiocyanate is 0.25 l/kg (Schulz, 1984).

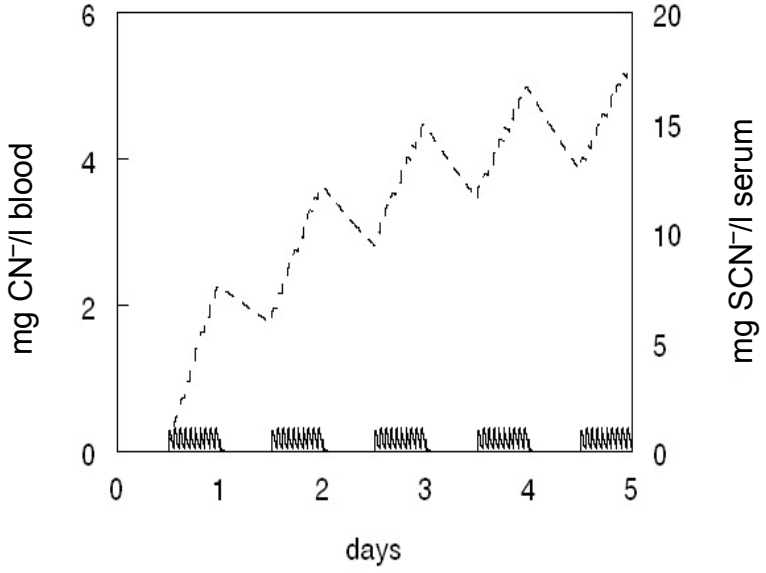
The results are presented in figure G.1 and G.2.

Figure G.1: Cyanide level in blood of pigs following bolus dosing of 1.2 mg CN^-/kgbw/d[a]



[a] —— CN^-, - - - SCN^-

Figure G.2: Cyanide level in blood of pigs following uptake of 1.2 mg CN^-/kgbw/d via drinking water[a]



[a] —— CN^-, - - - SCN^-

From Figures G.1 and G.2 it can be seen that, in the case of a bolus dose, cyanide in blood reaches much higher levels than when the dose is spread over a period of 12 hours. The maximum blood level in case of a bolus dosing appeared to be 2.9 mg/l, while in the case of application via drinking water the level was not higher than 0.32 mg/l. A blood level of more than 2 mg/l is potentially lethal and causes effects of severe intoxication.

The steady-state level of thiocyanate in plasma of juvenile pigs is estimated to be 16 mg SCN^-/l. In humans, thiocyanate levels in plasma of non-smokers may rise to 5 mg/l and in heavy smokers to 19 mg/l (Tsuge *et al*, 2000). So the blood level of thiocyanate in juvenile pigs dosed with 1.2 mg CN^-/kgbw/d is just at the upper end of the range of thiocyanate levels in blood, normally observed in the human population.

The behavioural effects in pigs resulting from bolus dosing of cyanide above 1 mg/kgbw/d were probably caused by repeated sublethal intoxications by cyanide. The claim of Jackson (1988a), that it was an effect on the thyroid due to thiocyanate accumulation in blood, which inhibits the iodine uptake in the thyroid, is not substantiated by the above simulation. It is true, that thiocyanate inhibits the iodide absorption by the thyroid, but this was compensated for by an increase of thyroid volume triggered by TSH from the pituitary. So it is unlikely that behavioural changes in pigs dosed with cyanide as a bolus of 1.2 mg/kg/d, are caused by increased thiocyanate levels in blood.

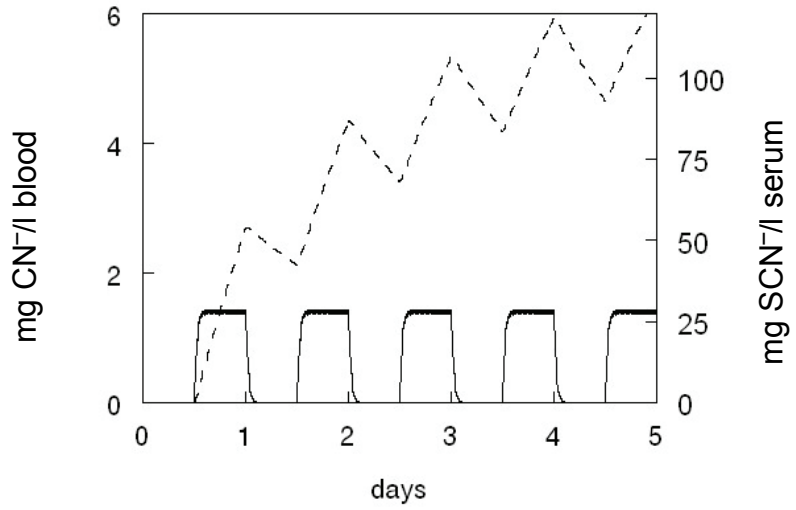
G.2 Blood levels of cyanide in rats' drinking water containing cyanide

A toxicokinetic model was developed for a rat dosed with 12.5 mg/kgbw/d via the drinking water (300 mg NaCN/l; 160 ppm CN^-/l) for 90 days (Hébert, 1993). It should be considered that the rat is quite prudent in food and drinking habits: it will take up toxic drinking water in small volumes, so as to avoid severe intoxication. Considering these peculiarities of the rat, the following assumptions were made for a toxicokinetic model:

- Cyanide given by gavage is absorbed in 15 minutes
- Cyanide given by drinking water is consumed in 100 equal volumes spaced over 12 h/d by periods of 7.2 minutes
- The turnover time of cyanide in rats is 20 minutes
- At this high-dose level, 68% of cyanide was converted to thiocyanate
- The turnover time of thiocyanate is 1 day
- Distribution volume and first-pass effect are similar to those of juvenile pigs

The concentration of cyanide and thiocyanate in blood over a period of 5 days is plotted in Figure G.3.

Figure G.3: Cyanide level in blood of rats following uptake of 12.5 mg CN^-/kgbw/d via drinking water[a]



[a] —— CN^-, - - - SCN^-

From Figure G.3 it can be seen that the cyanide concentration in blood will not exceed the level of 2 mg CN^-/l. Above a level of 3 mg/l blood, moderate to severe effects of intoxication will occur. This means that the level of 12 mg CN^-/kgbw/d (300 mg NaCN/l; 160 ppm CN^-/l) will hardly cause severe cyanide intoxication in rats. This was the highest dose level in the 90-day drinking-water study with NaCN in rats (Hébert, 1993).

APPENDIX H: ESTIMATION OF DAILY DOSE AND OCCUPATIONAL EXPOSURE LEVEL OF CYANIDE FROM THIOCYANATE LEVELS IN SERUM AND URINE

This estimation is based on the toxicokinetic data of Schulz (1984) on thiocyanate in humans and on the recommendations for human physiological parameters of the second edition of the European technical guidance document for risk assessment (ECB, 2003). The following parameters were used:

Body weight man:	70 kg
Inhalation volume (8 hour work day):	10 m^3
Retention of cyanide in the body:	50%
Half-life cyanide:	30 min
Turnover time cyanide:	43 min
Percent conversion cyanide into thiocyanate	80%
Half-life thiocyanate:	2.7 d
Turnover time thiocyanate:	3.9 d
Distribution volume thiocyanate:	0.25 l/kgbw
Urinary volume:	20 ml/kgbw/d
Creatinine excretion:	20 mg/kgbw/d
Molecular mass of cyanide	26
Molecular mass of thiocyanate:	58
Molecular mass of creatinine:	113.1

Thiocyanate excretion of 1 mg SCN^-/l urine is equivalent to a daily excretion of 0.02 mg/kgbw and has been formed from $0.02 \times (26/58)/0.8 = 0.011$ mg CN^-/kgbw/d. Because the retention of cyanide is 50% in the body, the total inhaled dose is $2 \times 0.011 = 0.022$ mg CN^-/kgbw/d. Since the human body weighs 70 kg, a total of $70 \times 0.022 = 1.54$ mg CN^- is inhaled in a volume of 10 m^3/d. This is equivalent to an exposure level in the working place of 0.154 mg CN^-/m^3.

Excretion of 1 mg SCN^-/d originates from $1 \times (26/58)/0.8 = 0.56$ mg CN^-/kgbw/d. Because the retention of cyanide in the body is 50%, the total inhaled dose during a working day is $2 \times 0.56 = 1.12$ CN^- in a volume of 10 m^3. This is equivalent to an exposure level of 0.112 mg CN^-/m^3.

A level of 1 mg SCN^-/l serum corresponds to a body burden of 0.25 mg SCN^-/kgbw, because of the distribution volume of 0.25 l/kgbw. Because the turnover (or residence) time is 3.9 days, a fraction of the body burden is excreted daily, i.e. $0.25/3.9 = 0.064$ mg SCN^-/kgbw/d. For a human being of 70 kgbw, this means an excretion of $1 \times 0.064 \times 70 = 4.5$ mg SCN^-/d. In the previous paragraph it is has been shown, that excretion of 1 mg SCN^-/d corresponds to an exposure level

in the workplace of 0.112 mg CN^-/m^3. Excretion of 4.5 mg SCN^-/d is equivalent to a cyanide exposure level in air of $4.5 \times 0.112 = 0.5$ mg CN^-/m^3. So 1 mg SCN^-/l serum implies a daily occupational exposure level of 0.5 mg CN^-/m^3.

According to the previous paragraph 1 mg SCN^-/l serum is equivalent to a daily occupational exposure level of 0.5 mg/m^3. This means that 1 µmol SCN^-/l serum (0.058 mg/l) corresponds to a daily occupational exposure level of 0.029 mg CN^-/m^3.

The above calculations are summarised in Table H.

Table H: Human exposure to cyanide estimated from thiocyanate levels

Thiocyanate (SCN^-) in urine or serum	Cyanide dose (mg CN^-/kgbw/d)	Exposure level (mg CN^-/m^3)
Urine		
1 mg/l	0.022	0.154
1 mg/d (excretion)	0.56	0.112
Serum		
1 mg/l	0.064	0.5
1 µmol/l	0.0037	0.029

Banerjee (1997) found a level of 316 µmol SCN^-/l serum in workers in the electroplating industry. So the estimated daily occupational exposure can be estimated from the previous paragraph and is estimated to be $316 \times 0.029 = 9.2$ mg CN^-/m^3. These levels did not cause goitre, but did cause some changes in thyroid hormone levels and an increase in TSH levels. Unfortunately, no information was provided on the iodine status of the workers. These levels are comparable to the peak levels of thiocyanate in serum of heavy smokers (Scheuermann *et al*, 1991 cited by Knudsen *et al* 2002; Tsuge *et al*, 2000).

APPENDIX J: AQUATIC TOXICITY OF CYANIDES

The following list (Table J) is sorted in alphabetical order by taxonomic group, effect concentration and species. The abbreviations used here follow (and have been adapted from) the US-EPA Ecotox database (US-EPA, 2003). Almost all data assigned CoR 4 were taken directly from the Ecotox database (references in Section 13.2). In several cases, reported concentrations were converted and standardised to µg CN^-/l.

J.1 Endpoint

BAF	Bioaccumulation factor: A value that is the ratio of the concentration of a chemical in the organism to that in the medium. Bioaccumulation refers to both uptake of dissolved chemicals from water (bioconcentration) and uptake from ingested food and sediment residues. BAF values are only reported in the terrestrial database. Values reported as BCF in pore water or hydroporic studies are reported in the Ecotox database as a BAF
BCF	Bioconcentration factor: A unitless value describing the degree to which a chemical can be concentrated in the tissues of an organism in the aquatic environment. At apparent equilibrium during the uptake phase of a bioconcentration test, the BCF is the concentration of a chemical in one or more tissues of the aquatic organism divided by the average concentration in the water. Alternatively, it is calculated from a ratio of rate constants at steady state, BCF = K1 (uptake) / K2 (elimination)
EC_{xx}	Effective concentration for xx% (median is for 50%) of organisms tested. Used when an effect other than death is the observed endpoint
EC_{50}*	Median effect concentration
ET_{50}	Median effective time: Time to effect or estimated mean survival time
IC_{xx}	Inhibition concentration: A point estimate of the toxicant concentration that would cause an xx% reduction in a non-lethal biological measurement
LC_{xx}	Lethal concentration: Statistically estimated concentration that is expected to be lethal to xx% (median is for 50%) of organisms tested. Death may be defined by the mortality, intoxification or population effect groups
LC_{50}*	LC value representing median tolerance limit (TL_m or TL_{50}) values with death as the measured endpoint
LD_{xx}	Lethal dose: A statistically estimated dose that is expected to be lethal to xx% of a group of organisms
LETC	Lethal threshold concentration: Toxicity curve asymptotic concentration indicating an incipient LC_{50} value. Acute lethal action has essentially ceased

LOEC/LOEL	Lowest-observed effect concentration or level that has a statistically significant adverse effect on the tested organisms. The minimum effective concentration (MEC) is coded as LOEC
LT_{xx}	Survival time: Time until xx% (mean is for 50%) of test organisms are dead
MATC	Maximum acceptable toxicant concentration: Hypothetical threshold concentration that is the geometric mean between the NOEC and LOEC concentration. The chronic value (ChV) is coded as MATC
NOEC/NOEL	No observed effect concentration or level: Highest concentration or dose producing effects not significantly different from responses of controls according to author's reported statistical test
NR-LETH	Near lethal: 100% mortality or 0% survival including algicidal and herbicidal effects. No statistically derived endpoint reported. This is only used in the aquatic database
NR-ZERO	Near zero mortality: 0% mortality or 100% survival of organisms. (No statistically derived endpoint reported). This is only used in the aquatic database
-	Not stated

J.2 Effect

ACC	Accumulation
AVO	Avoidance behaviour
BCM	Biochemical
BEH	Behaviour
DVP	Development
ENZ	Enzyme
FDB	Feeding behaviour
GEN	Genetics
GRO	Growth
HIS	Histology
HRM	Hormone
IMM	Immunological
ITX	Intoxication
MOR	Mortality
MPH	Morphology
NOC	No group code
PHY	Physiology
POP	Population
REP	Reproduction

J.3 Aquatic medium

FW	Freshwater
SW	Saltwater
-	Not stated

J.4 Type of exposure

C	Continuous
E	Lentic (static water system without measurable flow rate, e.g. lake)
F	Flow-through
P	Pulse (intermittent or fluctuating dosing)
R	Renewal
S	Static
-	Not stated

Table J: Aquatic toxicity records

Species	Endpoint	Effect	Concentration [a] ($\mu g\ CN^-/l$)	Medium	Duration	Unit	Exposure type	T (°C)	Reference [b]	CoR
Algae										
Algae, not further specified	-	PHY	20	SW	6	h	S	-	Niemi, 1972	3
Phytoplankton, not specified	NOEC	POP	< 100	FW	10	d	S	24	Shehata *et al*, 1988	3
Chlorophyta										
Scenedesmus quadricauda	-	MOR	10	-	-	-	S	-	Bringmann and Kühn, 1978b	4
Chlorococcales	NOEC	PHY	24	FW	24	h	S	20	Krebs, 1991	2
Chlorococcales	EC_{50}	PHY	45	FW	24	h	S	20	Krebs, 1991	2
Chlorococcales	EC_{50}	PHY	< 918	FW	-	-	S	20	Krebs, 1991	3
Chlamydomonas	NOEC	POP	≥ 10	-	10	d	S	25	Cairns *et al*, 1978	1
Chlamydomonas	NOEC	POP	≥ 10	FW	10	d	S	15	Cairns *et al*, 1978	1
Scenedesmus quadricauda	NOEC	POP	12	-	7	d	S	27	Bringmann and Kühn, 1980b	3
Scenedesmus quadricauda	LOEC	POP	12	-	8	d	S	27	Bringmann and Kühn, 1978b	4
Scenedesmus quadricauda	NOEC	POP	12	FW	-	-	-	-	Bringmann and Kühn, 1979	3
Scenedesmus quadricauda	NOEC	POP	12	FW	8	d	S	27	Bringmann and Kühn, 1978b	2
Scenedesmus quadricauda	NOEC	POP	12	-	-	-	S	-	Bringmann and Kühn, 1977b	3

[a] Several values have been converted

[b] Almost all references with CoR 4 cited by US-EPA, 2003

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration [a] (µg CN^-/l)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Scenedesmus quadricauda	LOEC	POP	160	FW	96	h	S	24	Bringmann and Kühn, 1959a	2
Ankistrodesmus falcatus	NOEC	POP	265	SW	10	d	S	25	Tscheu-Schlüter, 1983	2
Scenedesmus quadricauda	NOEC	POP	300	FW	10	d	S	24	Shehata *et al*, 1988	2
Ankistrodesmus falcatus	IC_{50}	POP	1,250	FW	10	d	-	25	Tscheu-Schlüter and Skibba, 1986	2
Ankistrodesmus falcatus	EC_{50}	POP	1,250	SW	10	d	S	25	Tscheu-Schlüter, 1983	2
Cryptomonadae										
Chilomonas paramecium	-	POP	480	-	48	h	-	-	Bringmann *et al*, 1980	2e
Chilomonas paramecium	-	POP	480	FW	-	-	-	-	Bringmann and Kühn, 1981	4
Cyanophyta										
Anacystis aeruginosa	-	MOR	30	-	-	-	S	-	Bringmann and Kühn, 1978b	4
Anacystis aeruginosa	-	MOR	8,000	-	24	h	S	-	Fitzgerald *et al*, 1952	4
Microcystis aeruginosa	NOEC	POP	28	FW	8	d	S	-	Bringmann and Kühn, 1978c	2
Anacystis aeruginosa	-	POP	70	-	8	d	S	27	Bringmann and Kühn, 1978b	4
Anabaena flos aquae	NOEC	POP	≥ 700	FW	10	d	S	30	Shehata *et al*, 1988	2
Diatomeae										
Nitzschia closterium	NOEC	POP	10	SW	72	h	S	21	Pablo *et al*, 1997a	2
Nitzschia closterium	EC_{50}	POP	57	SW	72	h	S	21	Pablo *et al*, 1997a	2

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration [a] (µg CN^-/l)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Navicula seminulum	EC_{50}	POP	258	FW	96	h	S	30	Academy of Natural Sciences, 1960	2
Phaeodactylum tricornutum	-	POP	260	SW	72	h	S	-	Florence and Stauber, 1986	4
Navicula seminulum	EC_{50}	POP	278	FW	96	h	S	28	Academy of Natural Sciences, 1960	2
Navicula seminulum	EC_{50}	POP	280	FW	96	h	S	22	Academy of Natural Sciences, 1960	2
Navicula seminulum	EC_{50}	POP	296	FW	96	h	S	22	Academy of Natural Sciences, 1960	2
Navicula seminulum	EC_{50}	POP	297	FW	96	h	S	30	Academy of Natural Sciences, 1960	2
Navicula seminulum	EC_{50}	POP	312	FW	96	h	S	28	Academy of Natural Sciences, 1960	2
Navicula seminulum	EC_{50}	POP	330	FW	96	h	S	22	Academy of Natural Sciences, 1960	2
Navicula seminulum	EC_{50}	POP	340	FW	96	h	S	30	Academy of Natural Sciences, 1960	2
Navicula seminulum	EC_{50}	POP	382	FW	96	h	S	22	Academy of Natural Sciences, 1960	2
Navicula seminulum	EC_{50}	POP	394	FW	96	h	S	28	Academy of Natural Sciences, 1960	2
Navicula seminulum	EC_{50}	POP	508	FW	96	h	S	30	Academy of Natural Sciences, 1960	2
Navicula seminulum	EC_{50}	POP	588	FW	96	h	S	28	Academy of Natural Sciences, 1960	2
Rhodophyta										
Plumaria elegans	-	~ DVP	10,000	SW	18	h	-	-	Boney *et al*, 1959	4
Champia parvula	NOEC	GRO	3.9	SW	14	d	R	20 - 22	Steele and Thursby, 1983	2
Champia parvula	MATC	GRO	5.5	SW	14	d	R	20 - 22	Steele and Thursby, 1983	2

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration [a] (µg CN^-/l)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Champia parvula	MATC	GRO	13.5	SW	14	d	R	20 - 22	Steele and Thursby, 1983	2
Plumaria elegans	NR-ZERO	MOR	10,000	SW	18	h	-	-	Boney *et al*, 1959	4
Champia parvula	MATC	REP	5.5	SW	14	d	R	20 - 22	Steele and Thursby, 1983	2
Champia parvula	MATC	REP	20.5	SW	14	d	R	20 - 22	Steele and Thursby, 1983	2
Champia parvula	MATC	REP	50.5	SW	14	d	R	20 - 22	Steele and Thursby, 1983	2
Champia parvula	-	REP	61	SW	14	d	R	20 - 22	Steele and Thursby, 1983	3
Amphibia										
Rana temporaria	-	AVO	260	FW	0.42	h	-	-	Costa, 1965a	3
Rana temporaria	-	AVO	260	FW	0.58	h	-	-	Costa, 1965a	3
Rana temporaria	-	AVO	2,600	FW	0.067	h	-	-	Costa, 1965a	3
Rana temporaria	-	AVO	2,600	FW	0.017	h	-	-	Costa, 1965a	3
Rana temporaria	-	AVO	2,600	FW	< 0.03	h	-	-	Costa, 1965a	3
Rana temporaria	-	AVO	2,600	FW	0.1	h	-	-	Costa, 1965a	3
Rana temporaria	-	AVO	2,600	FW	0.05	h	-	-	Costa, 1965a	3
Rana temporaria	-	AVO	130,000	FW	0.067	h	-	-	Costa, 1965a	3
Annelida										
Dinophilus gyrociliatus	LC_{50}	MOR	5,937	SW	96	h	R	21	Carr *et al*, 1986	2

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration [a] ($\mu g\ CN^-/l$)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Dinophilus gyrociliatus	LC_{50}	MOR	6,770	SW	72	h	R	21	Carr *et al*, 1986	2
Dinophilus gyrociliatus	LC_{50}	MOR	7,194	SW	48	h	R	21	Carr *et al*, 1986	2
Dinophilus gyrociliatus	LC_{50}	MOR	7,570	SW	96	h	R	21	Carr *et al*, 1986	2
Dinophilus gyrociliatus	LC_{50}	MOR	8,489	SW	72	h	R	21	Carr *et al*, 1986	2
Dinophilus gyrociliatus	LC_{50}	MOR	8,901	SW	24	h	R	21	Carr *et al*, 1986	2
Dinophilus gyrociliatus	LC_{50}	MOR	9,540	SW	48	h	R	21	Carr *et al*, 1986	2
Dinophilus gyrociliatus	LC_{50}	MOR	11,446	SW	24	h	R	21	Carr *et al*, 1986	2
Bacteria										
Escherichia coli	LOEC	~PHY	600	FW	48	h	S	27	Bringmann and Kühn, 1959a	3
Pseudomonas putida	-	POP	1	FW	24	h	S	25	Bringmann and Kühn, 1980b	2
Bacteria	NOEC	POP	9.2	FW	-	-	-	-	Shkodich, 1966	3
Cnidaria										
Hydra attenuata	LC_{50}	MOR	7,000	FW	48	h	S	11	Gillar, 1962	4
Hydra viridissima	NOEC	POP	≥ 200	FW	6	d	S	30	Rippon *et al*, 1992	2
Crustacea										
Amphipoda										
Gammarus pulex	-	AVO	260	FW	0.042	h	-	-	Costa, 1965b	3

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration[a] (µg CN^-/l)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Gammarus pulex	-	AVO	2,600	FW	0.067	h	-	-	Costa, 1965b	3
Gammarus pulex	-	AVO	2,600	FW	0.15	h	-	-	Costa, 1965b	3
Gammarus pulex	-	AVO	2,600	FW	0.017	h	-	-	Costa, 1965b	3
Gammarus pulex	-	AVO	13,000	FW	0.33	h	-	-	Costa, 1965b	3
Gammarus pseudolimnaeus	NOEC	GRO	3.9	FW	98	d	-	18	Oseid and Smith, 1979	2
Gammarus pseudolimnaeus	LOEC	GRO	8.7	FW	98	d	-	18	Oseid and Smith, 1979	2
Gammarus pseudolimnaeus	NOEC	GRO	20.2	FW	83	d	-	18	Oseid and Smith, 1979	2
Gammarus pseudolimnaeus	LOEC	GRO	30.8	FW	83	d	-	18	Oseid and Smith, 1979	2
Gammarus pseudolimnaeus	NR-LETH	MOR	≥ 53.0	FW	98	d	-	18	Oseid and Smith, 1979	3
Gammarus pseudolimnaeus	LETC	MOR	71.3	FW	12	d	-	18	Oseid and Smith, 1979	2
Gammarus pseudolimnaeus	LC_{50}	MOR	83.9	FW	96	h	F	-	Smith *et al*, 1979	4
Gammarus pseudolimnaeus	LC_{50}	MOR	163	FW	96	h	-	18	Oseid and Smith, 1979	2
Gammarus pseudolimnaeus	LC_{50}	MOR	170	FW	96	h	F	-	Smith *et al*, 1979	4
Gammarus pseudolimnaeus	LC_{50}	MOR	176	FW	96	h	F	-	Smith *et al*, 1979	4
Gammarus fasciatus	LC_{50}	MOR	900	FW	96	h	S	20	Ewell *et al*, 1986	2
Ampelisca abdita	LC_{50}	MOR	996	SW	-	-	-	-	Brix *et al*, 2000	2
Gammarus pulex	LT_{50}	MOR	1,200	FW	5	h	R	15	Abel and Garner, 1986	3

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration [a] (µg CN^-/l)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Gammarus pulex	LT_{50}	MOR	3,000	FW	1.1	h	R	15	Abel and Garner, 1986	3
Gammarus pulex	LT_{50}	MOR	6,000	FW	-	-	R	15	Abel and Garner, 1986	3
Gammarus pulex	LT_{50}	MOR	12,000	FW	0.75	h	R	15	Abel and Garner, 1986	3
Gammarus pulex	LT_{50}	MOR	30,000	FW	0.3	h	R	15	Abel and Garner, 1986	3
Gammarus pulex	-	MOR	130,000	FW	1.5	h	-	-	Costa, 1965b	3
Gammarus pseudolimnaeus	NOEC	POP	3.9	FW	98	d	-	18	Oseid and Smith, 1979	2
Gammarus pseudolimnaeus	LOEC	POP	8.7	FW	98	d	-	18	Oseid and Smith, 1979	2
Gammarus pseudolimnaeus	NOEC	POP	30.8	FW	83	d	-	18	Oseid and Smith, 1979	2
Gammarus pseudolimnaeus	LOEC	POP	40.5	FW	83	d	-	18	Oseid and Smith, 1979	2
Gammarus pseudolimnaeus	NOEC	REP	3.9	FW	98	d	-	18	Oseid and Smith, 1979	2
Gammarus pseudolimnaeus	LOEC	REP	8.7	FW	98	d	-	18	Oseid and Smith, 1979	2
Gammarus pseudolimnaeus	NOEC	REP	15.4	FW	83	d	-	18	Oseid and Smith, 1979	2
Gammarus pseudolimnaeus	LOEC	REP	20.2	FW	83	d	-	18	Oseid and Smith, 1979	2
Anostraca										
Artemia salina	LC_{50}	MOR	6,720	SW	24	h	-	-	Calleja *et al*, 1994	4
Artemia salina	IC_{50}	MOR	31,000	SW	24	h	S	-	Matthews, 1995	2

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration[a] (µg CN^-/l)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Branchiopoda										
Streptocephalus proboscideus	LC_{50}	MOR	2,140	FW	24	h	-	-	Calleja *et al*, 1994	4
Cladocera										
Daphnia pulex	EC_{50}	ITX	224	FW	24	h	S	20	Lilius *et al*, 1995	2
Daphnia magna	EC_{50}	ITX	234	FW	24	h	S	21	Lilius *et al*, 1994	2
Daphnia magna	EC_{50}	ITX	400	FW	24	h	-	-	Calleja *et al*, 1994	4
Daphnia magna	-	ITX	800	FW	48	h	S	23	Bringmann and Kühn, 1959a	3
Daphnia magna	LETC	ITX	< 1,806	FW	48	h	-	-	Anderson, 1946	3
Daphnia magna	EC_{50}	ITX	1,900	FW	24	h	S	20	Bringmann and Kühn, 1982	2
Daphnia pulex	LC_{50}	MOR	1	FW	48	h	S	25	Cairns *et al*, 1978	1
Daphnia pulex	LC_{50}	MOR	3	FW	24	h	S	25	Cairns *et al*, 1978	1
Daphnia magna	NR-ZERO	MOR	23.3	FW	48	h	S	22	Monsanto, 1981c	1
Daphnia magna	LC_{50}	MOR	39.8	FW	48	h	S	22	Monsanto, 1981c	1
Daphnia sp.	LC_{50}	MOR	79.7	FW	96	h	S	31.4	Sarkar, 1990	2
Daphnia magna	LC_{50}	MOR	82.6	FW	24	h	S	20	Monsanto, 1981c	1
Daphnia pulex	LC_{50}	MOR	83	FW	48	h	S	-	Lee, 1976	4
Daphnia magna	LC_{50}	MOR	90	FW	96	h	S	20	Ewell *et al*, 1986	2

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration [a] (µg CN^-/l)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Daphnia pulex	LC_{50}	MOR	91	FW	24	h	S	-	Lee, 1976	4
Daphnia magna	NR-ZERO	MOR	100	FW	48	h	C	11	Gillar, 1962	4
Daphnia pulex	LC_{50}	MOR	110	FW	48	h	S	20	Cairns *et al*, 1978	1
Daphnia pulex	LC_{50}	MOR	150	FW	24	h	S	20	Cairns *et al*, 1978	1
Daphnia sp.	LC_{50}	MOR	169	FW	96	h	S	26.5	Sarkar, 1990	2
Daphnia sp.	LC_{50}	MOR	173	FW	96	h	S	21.5	Sarkar, 1990	2
Daphnia magna	LC_{50}*	MOR	180	FW	96	h	S	-	Dowden and Bennett, 1965	4
Daphnia pulex	LC_{50}	MOR	180	FW	48	h	S	15	Cairns *et al*, 1978	1
Daphnia magna	LC_{50}	MOR	212	FW	24	h	S	21	Bringmann and Kühn, 1977a	2
Daphnia pulex	LC_{50}	MOR	320	FW	24	h	S	15	Cairns *et al*, 1978	1
Daphnia pulex	LC_{50}	MOR	330	FW	48	h	S	10	Cairns *et al*, 1978	1
Daphnia pulex	LC_{50}	MOR	330	FW	24	h	S	10	Cairns *et al*, 1978	1
Daphnia pulex	LC_{50}	MOR	330	FW	48	h	S	5	Cairns *et al*, 1978	1
Daphnia pulex	LC_{50}	MOR	420	FW	24	h	S	5	Cairns *et al*, 1978	1
Daphnia magna	LC_{50}*	MOR	460	FW	72	h	S	-	Dowden and Bennett, 1965	4
Daphnia magna	LC_{50}	MOR	960	FW	48	h	S	-	Qureshi *et al*, 1982	4
Daphnia magna	LOEC	MOR	1,000	FW	48	h	C	-	Mălăcea, 1966	4

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration[a] (µg CN^-/l)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Daphnia magna	LC_{50}*	MOR	1,300	FW	24	h	S	-	Dowden and Bennett, 1965	4
Daphnia magna	LC_{50}*	MOR	1,300	FW	48	h	S	-	Dowden and Bennett, 1965	4
Daphnia sp.	NR-LETH	MOR	1,593	FW	-	-	-	-	Lewis and Tarrant, 1960	3
Daphnia magna	EC_{50}	NOC	354	FW	24	h	-	20	Amodei and Azzoni, 1991	4
Daphnia magna	EC_{50}	NOC	430	FW	24	h	-	20	Amodei and Azzoni, 1991	4
Daphnia magna	EC_{50}	NOC	493	FW	24	h	-	20	Amodei and Azzoni, 1991	4
Daphnia magna	EC_{50}	NOC	639	FW	24	h	-	20	Amodei and Azzoni, 1991	4
Daphnia magna	EC_{50}	NOC	667	FW	24	h	-	20	Amodei and Azzoni, 1991	4
Moinodaphnia macleayi	NOEC	REP	5.8	FW	5	d	S	30	Rippon *et al*, 1992	2
Moinodaphnia macleayi	LOEC	REP	22	FW	5	d	S	30	Rippon *et al*, 1992	2
Copepoda										
Acartia clausi	LC_{50}	MOR	30	SW	-	-	-	-	Brix *et al*, 2000	2
Cyclops viridis	LC_{50}	MOR	78	FW	96	h	S	31.4	Sarkar, 1990	2
Diaptomus sp.	LC_{50}	MOR	82	FW	96	h	S	31.4	Sarkar, 1990	2
Diaptomus sp.	LC_{50}	MOR	166	FW	96	h	S	21.5	Sarkar, 1990	2
Cyclops viridis	LC_{50}	MOR	167	FW	96	h	S	26.5	Sarkar, 1990	2

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration [a] (µg CN^-/l)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Cyclops viridis	LC_{50}	MOR	169	FW	96	h	S	21.5	Sarkar, 1990	2
Diaptomus	LC_{50}	MOR	173	FW	96	h	S	26.5	Sarkar, 1990	2
Cyclops sp.	LC_{50}	MOR	2,050	FW	48	h	C	14	Gillar, 1962	4
Decapoda										
Cancer irroratus	LC_{50}	MOR	4.2	SW	96	h	F	-	Johns and Gentile, 1981	4
Cancer irroratus	LC_{50}	MOR	4.9	SW	96	h	-	-	Brix *et al*, 2000	3
Cancer irroratus	LC_{50}	MOR	5.7	SW	96	h	F	-	Johns and Gentile, 1981	4
Cancer irroratus	NR-LETH	MOR	22	SW	96	h	F	-	Johns and Gentile, 1981	4
Cancer magister	LC_{50}	MOR	51	SW	96	h	S	10	Brix *et al*, 2000	2
Cancer magister	LC_{50}	MOR	92	SW	96	h	S	10	Brix *et al*, 2000	2
Penaeus monodon	LC_{50}	MOR	110	SW	96	h	R	23	Pablo *et al*, 1997c	2
Cancer oregonensis	LC_{50}	MOR	111	SW	96	h	S	10	Brix *et al*, 2000	2
Cancer gracilis	LC_{50}	MOR	135	SW	96	h	S	10	Brix *et al*, 2000	2
Cancer gracilis	LC_{50}	MOR	153	SW	96	h	S	10	Brix *et al*, 2000	2
Cancer oregonensis	LC_{50}	MOR	154	SW	96	h	S	10	Brix *et al*, 2000	2
Pandalus montagui	LC_{50}	MOR	250	SW	48	h	R	-	Portmann and Wilson, 1971	3
Caridina nilotica	LC_{50}	MOR	316	FW	96	h	S	-	Mowbray, 1988	4

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration [a] (µg CN^-/l)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Cancer productus	LC_{50}	MOR	332	SW	96	h	S	10	Brix *et al*, 2000	2
Cancer productus	LC_{50}	MOR	345	SW	96	h	S	10	Brix *et al*, 2000	2
Carcinus maenas	LC_{50}	MOR	> 5,000	SW	48	h	R	-	Portmann and Wilson, 1971	3
Orconectes rusticus	NR-LETH	MOR	5,000	FW	96	h	S	12	Bills and Marking, 1988	2
Isopoda										
Asellus communis	NOEC	GRO	27.9	FW	112	d	-	18	Oseid and Smith, 1979	2
Asellus communis	LOEC	GRO	38.5	FW	112	d	-	18	Oseid and Smith, 1979	2
Asellus communis	NOEC	GRO	39.5	FW	98	d	-	18	Oseid and Smith, 1979	3
Asellus communis	NOEC	GRO	< 49.1	FW	115	d	-	18	Oseid and Smith, 1979	2
Asellus communis	LOEC	GRO	53.0	FW	98	d	-	18	Oseid and Smith, 1979	3
Asellus intermedius	LC_{50}	MOR	1,700	FW	96	h	S	20	Ewell *et al*, 1986	2
Asellus communis	LETC	MOR	1,825	FW	12	d	-	18	Oseid and Smith, 1979	2
Asellus communis	LETC	MOR	1,834	FW	11	d	F	-	Smith *et al*, 1979	4
Asellus communis	LC_{50}	MOR	2,211	FW	96	h	-	18	Oseid and Smith, 1979	2
Asellus communis	LC_{50}	MOR	2,328	FW	96	h	F	-	Smith *et al*, 1979	4
Asellus aquaticus	LC_{50}	MOR	2,680	FW	48	h	-	20	Tscheu-Schlüter and Skibba, 1986	2
Asellus communis	NOEC	POP	39.5	FW	98	d	-	18	Oseid and Smith, 1979	3

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration [a] (µg CN^-/l)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Asellus communis	NOEC	POP	< 49.1	FW	115	d	-	18	Oseid and Smith, 1979	2
Asellus communis	LOEC	POP	53.0	FW	98	d	-	18	Oseid and Smith, 1979	3
Asellus communis	NOEC	REP	39.5	FW	98	d	-	18	Oseid and Smith, 1979	3
Asellus communis	NOEC	REP	< 49.1	FW	115	d	-	18	Oseid and Smith, 1979	2
Asellus communis	LOEC	REP	53.0	FW	98	d	-	18	Oseid and Smith, 1979	3
Asellus communis	NOEC	REP	74.1	FW	112	d	-	18	Oseid and Smith, 1979	2
Asellus communis	LOEC	REP	96.3	FW	112	d	-	18	Oseid and Smith, 1979	2
Mysidacea										
Leptomysis mediterranea	LC_{50}	MOR	37	SW	96	h	S	-	Pavicic and Pihlar, 1982	2
Americamysis bahia	NOEC	MOR	49.5	SW	-	-	F	20 - 25	Lussier *et al*, 1985	2
Mysidopsis bigelowi	NR-ZERO	MOR	50	SW	96	h	S	-	Lussier, 1985	4
Leptomysis mediterranea	LC_{50}	MOR	88	SW	48	h	S	-	Pavicic and Pihlar, 1982	2
Mysidopsis bigelowi	LC_{50}	MOR	93.2	SW	96	h	S	-	Lussier, 1985	4
Americamysis bahia	LC_{50}	MOR	113	SW	96	h	F	20 - 25	Lussier *et al*, 1985	2
Mysidopsis bigelowi	LC_{50}	MOR	118	SW	-	-	-	-	Brix *et al*, 2000	2

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration [a] (µg CN^-/l)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Mysidopsis bigelowi	LC_{50}	MOR	124	SW	96	h	S	-	Lussier, 1985	4
Mysidopsis bigelowi	NR-LETH	MOR	300	SW	96	h	S	-	Lussier, 1985	4
Americamysis bahia	NOEC	REP	> 30.4	SW	-	-	F	20 - 25	Lussier *et al*, 1985	3
Americamysis bahia	MATC	REP	> 43	SW	-	-	F	20 - 25	Lussier *et al*, 1985	2
Echinoidea										
Anthocidaris crassispina	NOEC	DVP	125	SW	12	h	S	28	Kobayashi, 1971	2
Anthocidaris crassispina	LOEC	DVP	250	SW	12	h	S	28	Kobayashi, 1971	2
Patriella calcar	EC_{50}	HIS/MPH	0.03	SW				24	Mahadevan, 1986	3
Fish										
Osteichthyes not further specified	-	ITX	1,062	FW	-	-	F	-	Lewis and Tarrant, 1960	3
Apteronotidae										
Apteronotus albifrons	LOEC	PHY	14	FW	0.5	h	F	27	Thomas *et al*, 1996	3
Anguillidae										
Anguilla anguilla	-	AVO	1,300	FW	-	-	S	-	Costa, 1965c	3
Anguilla anguilla	-	AVO	1,300	FW	-	-	S	-	Costa, 1965c	3

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration [a] (µg CN^-/l)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Atherinidae										
Menidia menidia	NR-LETH	MOR	56	SW	96	h	F	-	Berry and Gardner, 1981	4
Menidia menidia	NR-LETH	MOR	56	SW	96	h	F	-	Berry and Gardner, 1981	4
Menidia menidia	LC_{50}	MOR	59	SW	96	h	S	-	Brix *et al*, 2000	4
Menidia menidia	LC_{50}	MOR	59.3	SW	96	h	F	-	Berry and Gardner, 1981	4
Atherinopsidae										
Menidia beryllina	LC_{50}	MOR	153	SW	-	-	S	20	Dawson *et al*, 1977	2
Centrarchidae										
Lepomis macrochirus	-	ACC	48	FW	2	h	S	-	Broderius, 1973	2
Micropterus salmoides	-	BEH	20	FW	24	h	F	22	Morgan, 1977	4
Micropterus salmoides	-	BEH	50	FW	24	h	F	22	Morgan, 1977	4
Lepomis macrochirus	-	BEH	5,000	FW	2	h	S	-	Applegate *et al*, 1957	4
Lepomis macrochirus	ET_{50}	ITX	149	FW	11.67	h	S	20	Doudoroff *et al*, 1966	2
Lepomis macrochirus	ET_{50}	ITX	164	FW	5.65	h	S	20	Doudoroff *et al*, 1966	2
Lepomis macrochirus	ET_{50}	ITX	212	FW	6.7	h	S	20	Doudoroff *et al*, 1966	2
Lepomis macrochirus	ET_{50}	ITX	221	FW	4.32	h	S	20	Doudoroff *et al*, 1966	2
Lepomis macrochirus	ET_{50}	ITX	279	FW	3.85	h	S	20	Doudoroff *et al*, 1966	2

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration a (µg CN^-/l)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Lepomis macrochirus	ET50	ITX	310	FW	3.25	h	S	20	Doudoroff *et al*, 1966	2
Lepomis macrochirus	ET50	ITX	366	FW	3.42	h	S	20	Doudoroff *et al*, 1966	2
Lepomis macrochirus	ET_{50}	ITX	482	FW	2.15	h	S	20	Doudoroff *et al*, 1966	2
Lepomis macrochirus	EC_{50}	ITX	597	FW	1.52	h	S	20	Doudoroff *et al*, 1966	2
Lepomis macrochirus	ET_{50}	ITX	780	FW	1.45	h	S	20	Doudoroff *et al*, 1966	2
Lepomis macrochirus	ET_{50}	ITX	867	FW	0.83	h	S	20	Doudoroff *et al*, 1966	2
Micropterus salmoides	-	ITX	1,328	FW	-	-	E	2.8	Lewis and Tarrant, 1960	3
Lepomis macrochirus	NOEC	MOR	8.8	FW	57	d	F	25	Kimball *et al*, 1978	2
Lepomis macrochirus	NR-ZERO	MOR	24	FW	96	h	S	22	Monsanto, 1981a	1
Lepomis macrochirus	LC_{10}	MOR	48	FW	289	d	F	25	Kimball *et al*, 1978	2
Lepomis macrochirus	LC_{50}	MOR	48	FW	96	h	S	18	Academy of Natural Sciences, 1960	3
Lepomis macrochirus	LC_{50}	MOR	61.6	FW	168	h	F	25.4	Cardwell *et al*, 1976	2
Lepomis macrochirus	LC50	MOR	65.9	FW	120	h	F	25.4	Cardwell *et al*, 1976	2
Lepomis macrochirus	NR-ZERO	MOR	70	FW	96	h	S	18	Cairns and Scheier, 1968	2
Lepomis macrochirus	LC_{50}	MOR	~ 70	FW	289	d	F	25	Kimball *et al*, 1978	3
Lepomis macrochirus	LC_{50}	MOR	71.2	FW	48	h	F	25.4	Cardwell *et al*, 1976	2
Lepomis macrochirus	LC_{50}	MOR	72.2	FW	96	h	F	15	Smith *et al*, 1978	2

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration [a] ($\mu g\ CN^-/l$)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Lepomis macrochirus	LC50	MOR	79.1	FW	24	h	F	25.4	Cardwell *et al*, 1976	**2**
Lepomis macrochirus	LC50	MOR	79.9	FW	96	h	F	8	Smith *et al*, 1978	**2**
Enneacanthus chaetodon	LT_{50}	MOR	80	FW	-	-	-	-	Department of Scientific and Industrial Research, 1953	4
Lepomis macrochirus	LC_{50}	MOR	83.9	FW	96	h	F	15	Smith *et al*, 1978	2
Lepomis macrochirus	LC_{50}	MOR	< 88.6	FW	96	h	F	10	Smith *et al*, 1978	3
Lepomis macrochirus	LC_{50}	MOR	95.3	FW	96	h	F	18	Smith *et al*, 1978	2
Lepomis macrochirus	LC_{50}	MOR	96.0	FW	96	h	F	25	Smith *et al*, 1978	2
Lepomis macrochirus	LC_{50}	MOR	97.2	FW	6	h	F	25.4	Cardwell *et al*, 1976	2
Micropterus salmoides	LC_{50}	MOR	101	FW	96	h	F	-	Smith *et al*, 1979	4
Lepomis macrochirus	LC_{50}	MOR	104	FW	96	h	F	20	Smith *et al*, 1978	2
Lepomis macrochirus	LETC	MOR	105	FW	7	h	F	25	Smith *et al*, 1978	2
Lepomis macrochirus	LC_{50}	MOR	109	FW	96	h	F	25	Smith *et al*, 1978	2
Lepomis macrochirus	LC_{50}	MOR	115	FW	2	h	F	25.4	Cardwell *et al*, 1976	2
Lepomis macrochirus	LC_{50}	MOR	116	FW	96	h	F	25	Smith *et al*, 1978	2
Lepomis macrochirus	LC_{50}	MOR	120	FW	96	h	S	30	Academy of Natural Sciences, 1960	2
Lepomis macrochirus	LC_{50}	MOR	121	FW	96	h	F	25	Smith *et al*, 1978	2

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration [a] (µg CN^-/l)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Lepomis macrochirus	LT_{50}	MOR	126	FW	10.92	h	S	-	Broderius, 1973	2
Lepomis macrochirus	LC_{50}	MOR	129	FW	96	h	S	22	Monsanto, 1981a	1
Lepomis macrochirus	LC_{50}*	MOR	132	FW	72	h	S	30	Cairns and Scheier, 1963	2
Lepomis macrochirus	LC_{50}*	MOR	132	FW	48	h	S	30	Cairns and Scheier, 1963	2
Lepomis macrochirus	LC_{50}*	MOR	132	FW	96	h	S	30	Cairns and Scheier, 1963	2
Lepomis cyanellus	-	MOR	133	FW	72	h	-	24.4	Lewis and Tarrant, 1960	3
Lepomis macrochirus	LC_{50}	MOR	135	FW	96	h	F	20	Doudoroff *et al*, 1966	2
Lepomis macrochirus	LC_{50}	MOR	140	FW	96	h	S	30	Academy of Natural Sciences, 1960	2
Lepomis macrochirus	LC_{50}*	MOR	140	FW	96	h	S	30	Cairns and Scheier, 1963	2
Lepomis macrochirus	LC_{50}*	MOR	140	FW	72	h	S	30	Cairns and Scheier, 1963	2
Lepomis macrochirus	LC_{50}	MOR	141	FW	24	h	S	22	Monsanto, 1981a	1
Lepomis macrochirus	LT_{50}	MOR	141	FW	5.88	h	S	-	Broderius, 1973	2
Lepomis macrochirus	LETC	MOR	143	FW	96	h	F	25	Smith *et al*, 1978	2
Lepomis macrochirus	LC_{50}*	MOR	150	FW	96	h	S	25	Henderson *et al*, 1961	2
Lepomis macrochirus	LC50*	MOR	154	FW	48	h	F	20	Doudoroff et al, 1966	2
Lepomis macrochirus	LC50*	MOR	154	FW	72	h	F	20	Doudoroff et al, 1966	2
Lepomis macrochirus	LC50*	MOR	156	FW	48	h	S	30	Cairns and Scheier, 1963	2

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration[a] ($\mu g\ CN^-/l$)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Lepomis macrochirus	LC_{50}	MOR	160	FW	48	h	-	-	Cairns *et al*, 1965	2
Lepomis macrochirus	LT_{50}	MOR	160	FW	5.85	h	S	-	Broderius, 1973	2
Lepomis macrochirus	LC_{50}	MOR	160	FW	24	h	S	15	Cairns *et al*, 1978	1
Lepomis macrochirus	LT_{50}	MOR	162	FW	4.3	h	S	-	Broderius, 1973	2
Lepomis macrochirus	LC_{50}*	MOR	164	FW	72	h	S	18	Cairns and Scheier, 1963	2
Lepomis macrochirus	LC_{50}*	MOR	168	FW	72	h	S	18	Cairns and Scheier, 1963	2
Lepomis macrochirus	LC_{50}*	MOR	168	FW	96	h	S	18	Cairns and Scheier, 1963	2
Lepomis macrochirus	LT_{50}	MOR	170	FW	351	min	-	-	Broderius, 1970	4
Lepomis macrochirus	LC_{50}	MOR	173	FW	1.5	h	F	25.4	Cardwell *et al*, 1976	2
Lepomis macrochirus	LC50	MOR	174	FW	-	-	S	23	Dawson et al, 1977	2
Micropterus dolomieui	LT50	MOR	175	FW	5	h	F	-	Burdick et al, 1958	3
Lepomis macrochirus	LC50*	MOR	176	FW	48	h	S	18	Cairns and Scheier, 1963	2
Lepomis macrochirus	LC50	MOR	180	FW	96	h	S	18	Academy of Natural Sciences, 1960	2
Lepomis macrochirus	LC50	MOR	180	FW	96	h	S	18	Cairns and Scheier, 1958	3
Lepomis macrochirus	LC50	MOR	180	FW	96	h	S	18	Cairns and Scheier, 1968	3
Lepomis macrochirus	LC50	MOR	180	FW	96	h	S	18	Academy of Natural Sciences, 1960	2

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration [a] ($\mu g\ CN^-/l$)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Lepomis macrochirus	LC_{50}	MOR	180	FW	96	h	S	-	Cairns and Scheier, 1959	2
Lepomis macrochirus	LC50*	MOR	180	FW	96	h	S	18	Cairns and Scheier, 1963	2
Lepomis macrochirus	LETC	MOR	187	FW	96	h	F	25	Smith *et al*, 1978	2
Lepomis macrochirus	LC_{50}*	MOR	188	FW	48	h	S	18	Cairns and Scheier, 1963	2
Lepomis macrochirus	LC_{50}	MOR	190	FW	24	h	S	30	Cairns *et al*, 1978	1
Lepomis macrochirus	LT_{50}	MOR	190	FW	4.33	h	S	-	Broderius, 1973	2
Micropterus salmoides	-	MOR	192	FW	3	h	F	25	Morgan and Kühn, 1974	3
Lepomis macrochirus	LT_{50}	MOR	196	FW	3.37	h	S		Broderius, 1973	2
Lepomis macrochirus	LETC	MOR	197	FW	96	h	F	20	Smith *et al*, 1978	2
Enneacanthus chaetodon	LT_{50}	MOR	200	FW	-	-	-	-	Department of Scientific and Industrial Research, 1953	4
Lepomis macrochirus	LT_{50}	MOR	200	FW	260	min	-	-	Broderius, 1970	4
Lepomis macrochirus	LETC	MOR	210	FW	796	h	F	25	Smith *et al*, 1978	2
Lepomis macrochirus	LC_{50}	MOR	220	FW	96	h	S	20	Cairns and Scheier, 1959	2
Lepomis macrochirus	LC_{50}	MOR	223	FW	96	h	F	25	Smith *et al*, 1978	2
Lepomis macrochirus	LC_{50}	MOR	228	FW	96	h	S	-	Cairns and Scheier, 1959	2
Lepomis macrochirus	NR-LETH	MOR	240	UH	96	h	S	18	Cairns and Scheier, 1968	2

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration [a] ($\mu g\ CN^-/l$)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Lepomis macrochirus	LC_{50}	MOR	240	FW	24	h	S	5	Cairns *et al*, 1978	1
Lepomis macrochirus	LC_{50}	MOR	261	FW	96	h	F	25	Smith *et al*, 1978	2
Lepomis macrochirus	LC_{50}	MOR	266	FW	96	h	F	25	Smith *et al*, 1978	2
Lepomis macrochirus	LC50	MOR	280	FW	48	h	S	-	Turnbull et al, 1954	3
Lepomis macrochirus	LC50	MOR	280	FW	24	h	S	-	Turnbull et al, 1954	2
Lepomis macrochirus	LC50	MOR	352	FW	96	h	F	20	Smith et al, 1978	2
Enneacanthus chaetodon	LT50	MOR	400	FW	-	-	-	-	Department of Scientific and Industrial	4
Lepomis cyanellus	LT100	MOR	531	FW	2.8	h	S	12.2 - 26.7	Bridges, 1958	3
Micropterus salmoides	LT100	MOR	531	FW	1.4	h	S	23.3 - 26.7	Bridges, 1958	3
Pomoxis annularis	-	MOR	≤ 600	FW	≤ 350	min	-	-	Renn, 1955	4
Pomoxis annularis	-	MOR	≤ 600	FW	≤ 350	min	F	-	Renn, 1955	4
Lepomis macrochirus	-	MOR	≤ 600	FW	≤ 350	min	F	-	Renn, 1955	4
Lepomis macrochirus	-	MOR	≤ 600	FW	≤ 350	min	-	-	Renn, 1955	4
Micropterus dolomieui	-	MOR	≤ 600	FW	≤ 350	min	-	-	Renn, 1955	4
Micropterus dolomieui	-	MOR	≤ 600	FW	≤ 350	min	F	-	Renn, 1955	4
Micropterus salmoides	-	MOR	≤ 600	FW	≤ 350	min	-	-	Renn, 1955	4
Lepomis macrochirus	NR-LETH	MOR	1,000	FW	96	h	S	12	Bills and Marking, 1988	2
Micropterus salmoides	-	MOR	1,328	FW	24	h	E	-	Lewis and Tarrant, 1960	3

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration [a] ($\mu g\ CN^-/l$)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Micropterus salmoides	-	PHY	4	FW	24	h	F	-	Morgan, 1977	4
Micropterus salmoides	-	PHY	10	FW	24	h	F	22	Morgan, 1979	3
Micropterus salmoides	-	PHY	10	FW	24	h	F	-	Morgan, 1977	4
Micropterus salmoides	-	PHY	10	FW	24	h	F	-	Morgan, 1976	4
Micropterus salmoides	-	PHY	10	FW	24	h	F	-	Morgan, 1977	4
Micropterus salmoides	-	PHY	16	FW	12	h	F	25	Morgan and Kühn, 1974	3
Micropterus salmoides	-	PHY	192	FW	1	h	F	25	Morgan and Kühn, 1974	3
Lepomis macrochirus	NOEC	REP	< 5	FW	289	d	F	25	Kimball *et al*, 1978	2
Characidae										
Aphyocharax rubripinnis	LT_{50}	MOR	80	FW	1,000	min	-	-	Department of Scientific and Industrial Research, 1953	4
Aphyocharax rubripinnis	LT_{50}	MOR	200	FW	-	-	-	-	Department of Scientific and Industrial Research, 1953	4
Aphyocharax rubripinnis	LT_{50}	MOR	400	FW	-	-	-	-	Department of Scientific and Industrial Research, 1953	4
Cichlidae										
Cichlasoma bimaculatum	NOEC	BEH	< 10	FW	36	d	F	-	Leduc, 1966	2
Cichlasoma bimaculatum	EC25	BEH	87	FW	36	d	F	25	Leduc, 1966	3

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration[a] (µg CN^-/l)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Cichlasoma bimaculatum	-	ENZ	100	FW	60	d	F	-	Brockway, 1963	4
Pomoxis nigromaculatus	LC_{50}	MOR	101	FW	96	h	F	-	Smith *et al*, 1979	4
Cichlasoma bimaculatum	NR-ZERO	MOR	110	FW	60	d	F	-	Brockway, 1963	4
Cichlasoma bimaculatum	LC_{50}	MOR	135	FW	48	h	F	-	Brockway, 1963	4
Cichlasoma bimaculatum	LC_{50}	MOR	180	FW	24	h	F		Brockway, 1963	4
Tilapia mossambica	LC_{50}	MOR	194	FW	96	h	S	31.4	Sarkar, 1990	2
Tilapia mossambica	LC_{50}	MOR	1,047	FW	96	h	S	26.5	Sarkar, 1990	2
Tilapia mossambica	LC_{50}	MOR	1,068	FW	96	h	S	21.5	Sarkar, 1990	2
Tilapia mossambica	-	PHY	50	FW	24	h	F	-	Morgan, 1977	4
Tilapia mossambica	-	PHY	50	FW	24	h	F	-	Morgan, 1976	4
Cyprinidae										
Cyprinidae, not further specified	-	ACC	10,000	-	5	h	-	-	Murachi *et al*, 1978	4
Phoxinus phoxinus	-	AVO	260	FW	-	-	S	-	Costa, 1966	3
Carassius auratus	-	AVO	260	FW	0.48	h	S	-	Costa, 1965c	3
Phoxinus phoxinus	-	AVO	1,300	FW	0.092	h	S	-	Costa, 1966	3
Carassius auratus	-	AVO	20,000	FW	0.17	h	F	-	Berry, 1976	4
Phoxinus phoxinus	-	BEH	100	FW	2.9	h	S	-	Wuhrmann and Woker, 1953	3

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration [a] (µg CN^-/l)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Phoxinus phoxinus	-	BEH	110	FW	0.52	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	120	FW	3.7	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	120	FW	5.8	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	150	FW	2	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	150	FW	0.27	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	160	FW	0.34	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	160	FW	1.75	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	160	FW	1.2	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	170	FW	0.46	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	180	FW	2.2	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	180	FW	1.7	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	200	FW	10.1	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	200	FW	0.73	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	210	FW	4.84	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	220	FW	0.08	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	220	FW	2.5	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	220	FW	0.2	h	S	-	Wuhrmann and Woker, 1953	3

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration [a] ($\mu g\ CN^-/l$)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Phoxinus phoxinus	-	BEH	230	FW	6	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	350	FW	4.2	h	S	-	Wuhrmann and Woker, 1953	3
Tinca tinca	-	BEH	460	FW	4.3	h	S	-	Wuhrmann and Woker, 1953	3
Tinca tinca	-	BEH	460	FW	3	h	S	-	Wuhrmann and Woker, 1953	3
Tinca tinca	-	BEH	470	FW	0.97	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	500	FW	0.45	h	S	-	Wuhrmann and Woker, 1953	3
Tinca tinca	-	BEH	500	FW	1.4	h	S	-	Wuhrmann and Woker, 1953	3
Tinca tinca	-	BEH	530	FW	5.9	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	530	FW	0.2	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	550	FW	1.2	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	550	FW	0.6	h	S	-	Wuhrmann and Woker, 1953	3
Tinca tinca	-	BEH	550	FW	1.7	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	620	FW	0.1	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	660	FW	0.85	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	790	FW	2.1	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	810	FW	0.2	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	840	FW	0.25	h	S	-	Wuhrmann and Woker, 1953	3

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration [a] (µg CN^-/l)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Phoxinus phoxinus	-	BEH	850	FW	0.21	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	860	FW	0.53	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	900	FW	0.72	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	910	FW	0.34	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	930	FW	0.06	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	940	FW	0.22	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	950	FW	0.07	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	1,030	FW	0.15	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	3,400	FW	0.19	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	3,630	FW	0.11	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	3,900	FW	0.17	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	3,900	FW	0.13	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	4,200	FW	0.35	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	4,300	FW	0.52	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	4,350	FW	0.07	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	4,380	FW	0.06	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	4,500	FW	0.41	h	S	-	Wuhrmann and Woker, 1953	3

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration [a] (µg CN^-/l)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Phoxinus phoxinus	-	BEH	4,600	FW	0.12	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	5,600	FW	0.06	h	S	-	Wuhrmann and Woker, 1953	3
Ptychocheilus oregonensis	-	BEH	10,000	FW	-	-	S	-	MacPhee and Ruelle, 1969	3
Ptychocheilus oregonensis	-	BEH	10,000	FW	-	-	S	-	MacPhee and Ruelle, 1969	3
Phoxinus phoxinus	-	BEH	17,400	FW	0.15	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	17,700	FW	0.43	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	18,700	FW	0.13	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	19,050	FW	0.35	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	19,300	FW	0.34	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	20,100	FW	0.06	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	20,600	FW	0.13	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	21,300	FW	0.06	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	21,400	FW	0.32	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	21,500	FW	0.06	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	31,300	FW	0.39	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	53,900	FW	0.31	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	84,000	FW	0.09	h	S	-	Wuhrmann and Woker, 1953	3

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration [a] (µg CN^-/l)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Phoxinus phoxinus	-	BEH	85,000	FW	0.17	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	87,700	FW	0.07	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	90,000	FW	0.12	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	93,000	FW	0.04	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	96,700	FW	0.05	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	101,000	FW	0.16	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	101,000	FW	0.18	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	101,500	FW	0.06	h	S	-	Wuhrmann and Woker, 1953	3
Phoxinus phoxinus	-	BEH	109,000	FW	0.09	h	S	-	Wuhrmann and Woker, 1953	3
Pimephales promelas	-	GEN	55.95	FW	24	h	F	25	Barron and Adelman, 1985	3
Cyprinodon variegatus	NOEC	GRO	29	SW	28	d	-	22.4	Schimmel, 1981	4
Pimephales promelas	NOEC	GRO	30	FW	30	d	F	25	Barron and Adelman, 1984	3
Cyprinodon variegatus	LOEC	GRO	44.6	SW	28	d	-	-	Schimmel, 1981	4
Pimephales promelas	-	GRO	55.9	FW	96	h	F	25	Barron and Adelman, 1985	3
Cyprinus carpio	LOEC	GRO	≤ 73	FW	42	d	F	20	Jee and Kang, 1999	4
Pimephales promelas	-	MOR	25	FW	30	d	F	-	Goode *et al*, 1976	4
Leuciscus idus melanotus	NR-ZERO	MOR	30.6	FW	-	h	-	-	Juhnke and Lüdemann, 1978	4

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration[a] ($\mu g\ CN^-/l$)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Pimephales promelas	LC_{50}*	MOR	34	FW	96	h	S	-	Goode *et al*, 1976	4
Rutilus rutilus	LC_{50}	MOR	42.4	FW	72	h	F	15.8	Solbé *et al*, 1985	2
Leucaspius delineatus	LOEC	MOR	60	FW	96	h	C	-	Mălăcea, 1966	4
Pimephales promelas	LC_{50}	MOR	60.6	FW	192	h	F	25.3	Cardwell *et al*, 1976	2
Pimephales promelas	LC_{50}	MOR	62.1	FW	144	h	F	25.3	Cardwell *et al*, 1976	2
Pimephales promelas	LC_{50}	MOR	63.7	FW	120	h	F	25.3	Cardwell *et al*, 1976	2
Pimephales promelas	LT_{50}	MOR	75.4	FW	33	h	F	25.3	Cardwell *et al*, 1976	2
Pimephales promelas	LC_{50}	MOR	78.6	FW	96	h	F	25	Smith *et al*, 1978	2
Pimephales promelas	LC_{50}	MOR	79.4	FW	96	h	F	20	Smith *et al*, 1978	2
Danio rerio	LT_{50}	MOR	80	FW	-	-	-	-	Department of Scientific and Industrial Research, 1953	4
Puntius cumingii	LT_{50}	MOR	80	FW	-	-	-	-	Department of Scientific and Industrial Research, 1953	4
Tanichthys albonubes	LT_{50}	MOR	80	FW	-	-	-	-	Department of Scientific and Industrial Research, 1953	4
Phoxinus phoxinus	LT_{50}	MOR	80	FW	-	-	-	-	Department of Scientific and Industrial Research, 1953	4
Pimephales promelas	LETC	MOR	88.1	FW	35	d	F	-	Smith *et al*, 1978	3

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration [a] (µg CN^-/l)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Pimephales promelas	LC_{50}	MOR	95.4	FW	96	h	F	20	Smith *et al*, 1978	2
Pimephales promelas	LC_{50}	MOR	96.1	FW	6	h	F	25.3	Cardwell *et al*, 1976	2
Pimephales promelas	LC_{50}	MOR	102	FW	96	h	F	25	Smith *et al*, 1978	2
Pimephales promelas	LC_{50}	MOR	104	FW	96	h	F	25	Smith *et al*, 1978	2
Pimephales promelas	LC_{50}	MOR	104	FW	3	h	F	25.3	Cardwell *et al*, 1976	2
Pimephales promelas	LETC	MOR	109	FW	96	h	F	25	Smith *et al*, 1978	2
Pimephales promelas	LC_{50}	MOR	109	FW	96	h	F	25	Smith *et al*, 1978	2
Pimephales promelas	LETC	MOR	112	FW	6	d	F	25	Smith *et al*, 1978	2
Pimephales promelas	LC_{50}	MOR	113	FW	96	h	F	20	Broderius *et al*, 1977	2
Pimephales promelas	LETC	MOR	114	FW	10	d	F	-	Smith *et al*, 1978	3
Pimephales promelas	LC_{50}	MOR	115	FW	96	h	F	25	Smith *et al*, 1978	2
Pimephales promelas	LC_{50}	MOR	115	FW	2.5	h	F	25.3	Cardwell *et al*, 1976	2
Pimephales promelas	LC_{50}	MOR	116	FW	96	h	F	25	Smith *et al*, 1978	2
Pimephales promelas	LC_{50}	MOR	117	FW	96	h	F	15	Smith *et al*, 1978	2
Pimephales promelas	LC_{50}	MOR	117	FW	96	h	F	25	Smith *et al*, 1978	2
Pimephales promelas	LC_{50}	MOR	117	FW	96	h	F	15	Smith *et al*, 1978	2
Pimephales promelas	LC_{50}	MOR	119	FW	96	h	F	20	Broderius *et al*, 1977	2

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration [a] ($\mu g\ CN^-/l$)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Pimephales promelas	LC_{50}	MOR	120	FW	96	h	F	25	Broderius and Smith, 1979	2
Pimephales promelas	LC_{50}	MOR	120	FW	96	h	F	20	Smith *et al*, 1978	2
Pimephales promelas	LC_{50}	MOR	120	FW	96	h	F	25	Broderius and Smith, 1979	3
Pimephales promelas	LETC	MOR	121	FW	96	h	F	15	Smith *et al*, 1978	2
Pimephales promelas	LC_{50}	MOR	123	FW	96	h	F	20	Smith *et al*, 1978	2
Pimephales promelas	LC_{50}	MOR	124	FW	96	h	F	25	Smith *et al*, 1978	2
Pimephales promelas	LC_{50}	MOR	126	FW	96	h	F	20	Smith *et al*, 1978	2
Pimephales promelas	LC_{50}	MOR	128	FW	96	h	F	20	Broderius *et al*, 1977	2
Pimephales promelas	LC_{50}	MOR	128	FW	96	h	F	20	Broderius *et al*, 1977	2
Pimephales promelas	LC_{50}	MOR	132	FW	96	h	F	20	Smith *et al*, 1978	2
Notemigonus crysoleucas	-	MOR	133	FW	72	h	-	24.4	Lewis and Tarrant, 1960	3
Carassius auratus	LC_{50}	MOR	139	FW	336	h	F	25	Cardwell *et al*, 1976	2
Rutilus rutilus	LC_{50}	MOR	145	FW	48	h	C	12	Gillar, 1962	4
Pimephales promelas	LC_{50}	MOR	146	FW	96	h	F	20	Broderius *et al*, 1977	2
Carassius auratus	LC_{50}	MOR	148	FW	298	h	F	25	Cardwell *et al*, 1976	2
Pimephales promelas	LC_{50}	MOR	151	FW	96	h	F	30	Smith *et al*, 1978	2
Pimephales promelas	LC_{50}	MOR	151	FW	96	h	F	20	Broderius *et al*, 1977	2

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration [a] ($\mu g\ CN^-/l$)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Pimephales promelas	LC_{50}	MOR	154	FW	96	h	F	25	Smith *et al*, 1978	2
Pimephales promelas	LETC	MOR	156	FW	96	h	F	25	Smith *et al*, 1978	2
Carassius auratus	LC_{50}	MOR	158	FW	168	h	F	25	Cardwell *et al*, 1976	2
Pimephales promelas	LC_{50}	MOR	159	FW	96	h	F	10	Smith *et al*, 1978	2
Pimephales promelas	LC_{50}	MOR	> 161	FW	96	h	F	5	Smith *et al*, 1978	3
Carassius auratus	LC_{50}	MOR	164	FW	120	h	F	25	Cardwell *et al*, 1976	2
Pimephales promelas	LC_{50}	MOR	168	FW	96	h	F	20	Smith *et al*, 1978	2
Carassius auratus	LC_{50}	MOR	169	FW	96	h	F	25	Cardwell *et al*, 1976	2
Pimephales promelas	LC_{50}	MOR	170	FW	96	h	S	20	Ewell *et al*, 1986	2
Pimephales promelas	LC_{50}	MOR	173	FW	1.5	h	F	25.3	Cardwell *et al*, 1976	2
Pimephales promelas	LETC	MOR	173	FW	96	h	F	25	Smith *et al*, 1978	2
Carassius auratus	LC_{50}	MOR	175	FW	24	h	F	25	Cardwell *et al*, 1976	2
Danio rerio	LC_{50}	MOR	176	FW	48	h	F	20	Slooff, 1979	2
Pimephales promelas	LC_{50}	MOR	177	FW	96	h	F	25	Smith *et al*, 1978	2
Carassius auratus	LC_{50}	MOR	183	FW	48	h	F	25	Cardwell *et al*, 1976	2
Pimephales promelas	LC_{50}	MOR	184	FW	96	h	F	15	Smith *et al*, 1978	2
Carassius auratus	LC_{50}	MOR	186	FW	36	h	F	25	Cardwell *et al*, 1976	2

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration [a] ($\mu g\ CN^-/l$)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Pimephales promelas	LC_{50}	MOR	189	FW	96	h	F	25	Smith *et al*, 1978	2
Rhinichthys atratulatus atratulatus	LT_{50}	MOR	~ 190	FW	48	h	-	-	Burdick and Lipschuetz, 1950	3
Rhinichthys atratulatus atratulatus	NR-LETH	MOR	~ 190	FW	76	h	-	-	Burdick and Lipschuetz, 1950	3
Semotilus atromaculatus atromaculatus	NR-LETH	MOR	~ 190	FW	76	h	-	-	Burdick and Lipschuetz, 1950	3
Semotilus atromaculatus atromaculatus	LT_{50}	MOR	~ 190	FW	48	h	-	-	Burdick and Lipschuetz, 1950	3
Pimephales promelas	LC_{50}	MOR	195	FW	96	h	F	25	Smith *et al*, 1978	2
Cirrhinus mrigala	LC_{50}	MOR	197	FW	96	h	S	31.4	Sarkar, 1990	2
Labeo rohita	LC_{50}	MOR	199	FW	96	h	S	31.4	Sarkar, 1990	2
Phoxinus phoxinus	LT_{50}	MOR	200	FW	~ 100	min	-	-	Department of Scientific and Industrial Research, 1953	4
Puntius cumingii	LT_{50}	MOR	200	FW	-	-	-	-	Department of Scientific and Industrial Research, 1953	4
Tanichthys albonubes	LT_{50}	MOR	200	FW	-	-	-	-	Department of Scientific and Industrial Research, 1953	4

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration [a] ($\mu g\ CN^-/l$)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Danio rerio	LT_{50}	MOR	200	FW	-	-	-	-	Department of Scientific and Industrial Research, 1953	4
Phoxinus phoxinus	LOEC	MOR	200	FW	96	h	C	-	Mălăcea, 1966	4
Leuciscus idus melanotus	LC_{50}	MOR	209	FW	96	h	-	20	Tscheu-Schlüter and Skibba, 1986	2
Carassius auratus	LC_{50}	MOR	214	FW	12	h	F	25	Cardwell *et al*, 1976	2
Labeo calbasu	LC_{50}	MOR	215	FW	96	h	S	31.4	Sarkar, 1990.	2
Rhinichthys atratulatus atratulatus	LC_{50}	MOR	220	FW	24	h	F	-	Lipschuetz and Cooper, 1955	2
Pimephales promelas	LC_{50}*	MOR	230	FW	96	h	S	25	Henderson *et al*, 1961	2
Pimephales promelas	LC_{50}	MOR	230	FW	96	h	S	20	Doudoroff, 1956	2
Carassius auratus	LC_{50}	MOR	237	FW	24	h	F	25	Cardwell *et al*, 1976	2
Pimephales promelas	LC_{50}*	MOR	240	FW	48	h	-	-	Black, 1957	4
Pimephales promelas	LC_{50}	MOR	240	FW	48	h	S	20	Doudoroff, 1956	3
Leuciscus idus melanotus	NR-ZERO	MOR	244	FW	-	h	-	-	Juhnke and Lüdemann, 1978	4
Labeo bata	LC_{50}	MOR	250	FW	96	h	S	31.4	Sarkar, 1990	2
Pimephales promelas	LC_{50}	MOR	250	FW	24	h	S	20	Doudoroff, 1956	2
Pimephales promelas	LC_{50}	MOR	262	FW	96	h	F	20	Smith *et al*, 1978	2

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration [a] ($\mu g\ CN^-/l$)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Leuciscus cephalus	NR-LETH	MOR	266	FW	4.5	h	F	12-14	Wuhrmann and Woker, 1948	3
Leuciscus idus melanotus	LC_{50}	MOR	275	FW	-	h	-	-	Juhnke and Lüdemann, 1978	4
Carassius auratus	LC_{50}	MOR	280	FW	24	h	S	30	Cairns *et al*, 1978	1
Catla catla	LC_{50}	MOR	295	FW	96	h	S	31.4	Sarkar, 1990	2
Rhinichthys atratulatus atratulatus	NR-LETH	MOR	~ 300	FW	29	h	-	-	Burdick and Lipschuetz, 1950	3
Cyprinodon variegatus	LC_{50}	MOR	300	SW	96	h	-	-	Brix *et al*, 2000	2
Semotilus atromaculatus atromaculatus	NR-LETH	MOR	300	FW	-	-	-	-	Burdick and Lipschuetz, 1950	3
Rhinichthys atratulatus atratulatus	LT_{50}	MOR	~ 300	FW	6.5	h	-	-	Burdick and Lipschuetz, 1950	3
Semotilus atromaculatus atromaculatus	NR-LETH	MOR	~ 300	FW	29	h	-	-	Burdick and Lipschuetz, 1950	3
Notemigonus crysoleucas	LC_{50}	MOR	300	FW	24	h	S	30	Cairns *et al*, 1978	1
Semotilus atromaculatus atromaculatus	LT_{50}	MOR	300	FW	6.5	h	-	-	Burdick and Lipschuetz, 1950	3
Pimephales promelas	LT_{50}	MOR	301	FW	165	min	F	-	Smith *et al*, 1979	4
Notemigonus crysoleucas	LC_{50}	MOR	310	FW	24	h	S	15	Cairns *et al*, 1978	1

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration [a] ($\mu g\ CN^-/l$)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Carassius auratus	LC_{50}	MOR	316	FW	8	h	F	25	Cardwell *et al*, 1976	2
Leuciscus idus melanotus	NR-LETH	MOR	337	FW		h	-	-	Juhnke and Lüdemann, 1978	4
Pimephales promelas	LC_{50}	MOR	339	FW	96	h	F	15.2	Smith *et al*, 1978	2
Pimephales promelas	LT_{50}	MOR	348	FW	172	min	F	-	Smith *et al*, 1979	4
Pimephales promelas	LC_{50}*	MOR	350	FW	96	h	S	25	Henderson *et al*, 1961	2
Leuciscus cephalus	NR-LETH	MOR	351	FW	4.8	h	F	12 - 14	Wuhrmann and Woker, 1948	3
Leuciscus cephalus	NR-LETH	MOR	351	FW	1.6	h	F	12 - 14	Wuhrmann and Woker, 1948	3
Leuciscus cephalus	NR-LETH	MOR	351	FW	0.8	h	F	12 - 14	Wuhrmann and Woker, 1948	3
Leuciscus cephalus	NR-LETH	MOR	351	FW	1.2	h	F	12 - 14	Wuhrmann and Woker, 1948	3
Leuciscus cephalus	NR-LETH	MOR	351	FW	0.9	h	F	12 - 14	Wuhrmann and Woker, 1948	3
Pimephales promelas	LT_{50}	MOR	382	FW	164	min	F	-	Smith *et al*, 1979	4
Pimephales promelas	LT_{50}	MOR	382	FW	198	min	F	-	Smith *et al*, 1979	4
Pimephales promelas	LT_{50}	MOR	390	FW	238	min	F	-	Smith *et al*, 1979	4
Puntius cumingii	LT_{50}	MOR	400	FW	-	-	-	-	Department of Scientific and Industrial Research, 1953	4
Danio rerio	LT_{50}	MOR	400	FW	-	-	-	-	Department of Scientific and Industrial Research, 1953	4

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration [a] ($\mu g\ CN^-/l$)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Phoxinus phoxinus	LT_{50}	MOR	400	FW	-	-	-	-	Department of Scientific and Industrial Research, 1953	4
Tanichthys albonubes	LT_{50}	MOR	400	FW	-	min	-	-	Department of Scientific and Industrial Research, 1953	4
Pimephales promelas	LT_{50}	MOR	401	FW	166	min	F	-	Smith *et al*, 1979	4
Tanichthys albonubes	LC_{50}	MOR	420	-	48	h	-	-	Kitamura, 1990	3
Tanichthys albonubes	LC_{50}	MOR	420	-	48	h	-	-	Kitamura, 1990	3
Tanichthys albonubes	LC_{50}	MOR	420	-	48	h	-	-	Kitamura, 1990	3
Tanichthys albonubes	LC_{50}	MOR	440	-	48	h	-	-	Kitamura, 1990	3
Danio rerio	LC_{50}	MOR	440	FW	48	h	F	-	Slooff, 1978	4
Carassius auratus	LC_{50}	MOR	440	FW	24	h	S	15	Cairns *et al*, 1978	1
Danio rerio	LC_{50}	MOR	440	FW	48	h	F	-	Slooff, 1979	3
Carassius auratus	LC_{50}	MOR	455	FW	6	h	F	25	Cardwell *et al*, 1976	2
Pimephales promelas	LT_{50}	MOR	464	FW	160	min	F	-	Smith *et al*, 1979	4
Pimephales promelas	LT_{50}	MOR	466	FW	119	min	F	-	Smith *et al*, 1979	4
Rhodeus sericeus amarus	LOEC	MOR	470	FW	96	h	C	-	Mălăcea, 1966	4
Danio rerio	LC_{50}	MOR	490	FW	96	h	-	24	Cairns *et al*, 1965	2

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration [a] (µg CN^-/l)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Danio rerio	LC_{50}	MOR	490	FW	24	h	-	24	Cairns *et al*, 1965	2
Danio rerio	LC_{50}	MOR	490	FW	48	h	-	24	Cairns *et al*, 1965	2
Pimephales promelas	LT_{50}	MOR	493	FW	107.5	min	F	-	Smith *et al*, 1979	4
Phoxinus phoxinus	LT_{50}	MOR	500	FW	1.33	h	S	-	Mălăcea, 1968	3
Leuciscus cephalus [c]	LOEC	MOR	500	FW	-	-	S	13	Wuhrmann and Woker, 1948	3
Pimephales promelas	LT_{50}	MOR	512	FW	184	min	F	-	Smith *et al*, 1979	4
Leuciscus idus melanotus	LC_{50}	MOR	520	FW	-	-		-	Juhnke and Lüdemann, 1978	4
Cyprinus carpio	LT_{100}	MOR	531	FW	11	h	S	26.1 - 26.7	Bridges, 1958	3
Carassius auratus	LT_{100}	MOR	531	FW	46	h	S	25.6 - 26.1	Bridges, 1958	3
Pimephales promelas	LT_{50}	MOR	536	FW	128	min	F	-	Smith *et al*, 1979	4
Notemigonus crysoleucas	LC_{50}	MOR	540	FW	24	h	S	5	Cairns *et al*, 1978	1
Danio rerio	NR-LETH	MOR	560	FW	24	h	-	24	Cairns *et al*, 1965	2
Leuciscus idus melanotus	NR-LETH	MOR	581	FW	-	-	-	-	Juhnke and Lüdemann, 1978	4
Pimephales promelas	LT_{50}	MOR	583	FW	88	min	F	-	Smith *et al*, 1979	4
Pimephales promelas	LT_{50}	MOR	59	FW	79	min	F	-	Smith *et al*, 1979	4
Pimephales promelas	LT_{50}	MOR	596	FW	179	min	F	-	Smith *et al*, 1979	4
Pimephales promelas	-	MOR	≤ 600	FW	≤ 350	min	-	-	Renn, 1955	4

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration [a] (µg CN^-/l)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Cyprinus carpio	NR-LETH	MOR	600	FW	72	h	S	16	Nehring, 1964	3
Notemigonus crysoleucas	-	MOR	≤ 600	FW	≤ 350	min	-	-	Renn, 1955	4
Carassius auratus	LC_{50}	MOR	602	FW	4	h	F	25	Cardwell *et al*, 1976	2
Pimephales promelas	LT_{50}	MOR	606	FW	62	min	F	-	Smith *et al*, 1979	4
Pimephales promelas	LT_{50}	MOR	619	FW	119	min	F	-	Smith *et al*, 1979	4
Leuciscus cephalus	NR-LETH	MOR	637	FW	2.6	h	F	12 - 14	Wuhrmann and Woker, 1948	3
Pimephales promelas	LT_{50}	MOR	664	FW	166	min	F	-	Smith *et al*, 1979	4
Pimephales promelas	LT_{50}	MOR	674	FW	138	min	F	-	Smith *et al*, 1979	4
Pimephales promelas	LT_{50}	MOR	703	FW	124	min	F	-	Smith *et al*, 1979	4
Pimephales promelas	LT_{50}	MOR	710	FW	69	min	F	-	Smith *et al*, 1979	4
Pimephales promelas	LT_{50}	MOR	713	FW	102	min	F	-	Smith *et al*, 1979	4
Pimephales promelas	LT_{50}	MOR	736	FW	154	min	F	-	Smith *et al*, 1979	4
Pimephales promelas	LT_{50}	MOR	794	FW	114	min	F	-	Smith *et al*, 1979	4
Pimephales promelas	LT_{50}	MOR	797	FW	45	min	F	-	Smith *et al*, 1979	4
Cirrhinus mrigala	LC_{50}	MOR	807	FW	96	h	S	21.5	Sarkar, 1990	2
Pimephales promelas	LT_{50}	MOR	820	FW	146	min	F	-	Smith *et al*, 1979	4
Pimephales promelas	LT_{50}	MOR	836	FW	59	min	F	-	Smith *et al*, 1979	4

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration [a] ($\mu g\ CN^-/l$)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Cirrhinus mrigala	LC_{50}	MOR	839	FW	96	h	S	26.5	Sarkar, 1990	2
Pimephales promelas	LT_{50}	MOR	905	FW	68	min	F	-	Smith *et al*, 1979	4
Catla catla	LC_{50}	MOR	919	FW	96	h	S	26.5	Sarkar, 1990	2
Pimephales promelas	LT_{50}	MOR	920	FW	33.5	min	F	-	Smith *et al*, 1979	4
Pimephales promelas	LT_{50}	MOR	933	FW	92.5	min	F	-	Smith *et al*, 1979	4
Catla catla	LC_{50}	MOR	935	FW	96	h	S	21.5	Sarkar, 1990	2
Pimephales promelas	LT_{50}	MOR	946	FW	44	min	F	-	Smith *et al*, 1979	4
Labeo bata	LC_{50}	MOR	998	FW	96	h	S	21.5	Sarkar, 1990	2
Pimephales promelas	LT_{50}	MOR	1,001	FW	117	min	F	-	Smith *et al*, 1979	4
Labeo calbasu	LC_{50}	MOR	1,030	FW	96	h	S	26.5	Sarkar, 1990	2
Labeo rohita	LC_{50}	MOR	1,036	FW	96	h	S	21.5	Sarkar, 1990	2
Labeo rohita	LC_{50}	MOR	1,046	FW	96	h	S	26.5	Sarkar, 1990	2
Labeo bata	LC_{50}	MOR	1,046	FW	96	h	S	26.5	Sarkar, 1990	2
Labeo calbasu	LC_{50}	MOR	1,052	FW	96	h	S	21.5	Sarkar, 1990	2
Leuciscus cephalus	NR-LETH	MOR	1,062	FW	1.2	h	F	12 - 14	Wuhrmann and Woker, 1948	3
Pimephales promelas	LT_{50}	MOR	1,066	FW	53	min	F	-	Smith *et al*, 1979	4
Pimephales promelas	LT_{50}	MOR	1,070	FW	57	min	F	-	Smith *et al*, 1979	4

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration [a] ($\mu g\ CN^-/l$)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Pimephales promelas	LT_{50}	MOR	1,076	FW	96.5	min	F	-	Smith *et al*, 1979	4
Pimephales promelas	LT_{50}	MOR	1,176	FW	26.5	min	F	-	Smith *et al*, 1979	4
Pimephales promelas	LT_{50}	MOR	1,290	FW	84.5	min	F	-	Smith *et al*, 1979	4
Pimephales promelas	LT_{50}	MOR	1,330	FW	74.5	min	F	-	Smith *et al*, 1979	4
Pimephales promelas	LT_{50}	MOR	1,387	FW	26.5	min	F	-	Smith *et al*, 1979	4
Pimephales promelas	LT_{50}	MOR	1,423	FW	49	min	F	-	Smith *et al*, 1979	4
Pimephales promelas	LT_{50}	MOR	1,698	FW	40.5	min	F	-	Smith *et al*, 1979	4
Pimephales promelas	LT_{50}	MOR	1,700	FW	69	min	F	-	Smith *et al*, 1979	4
Pimephales promelas	LT_{50}	MOR	1,737	FW	22	min	F	-	Smith *et al*, 1979	4
Pimephales promelas	LT_{50}	MOR	2,090	FW	38.5	min	F	-	Smith *et al*, 1979	4
Leuciscus cephalus	NR-LETH	MOR	2,098	FW	1	h	F	12 - 14	Wuhrmann and Woker, 1948	3
Carassius auratus	LC_{50}	MOR	3,250	FW	24	h	S	5	Cairns *et al*, 1978	1
Ptychocheilus oregonensis	-	MOR	4,000	FW	24	h	S	-	MacPhee and Ruelle, 1969	3
Leuciscus cephalus	NR-LETH	MOR	8,498	FW	1.2	h	F	12 - 14	Wuhrmann and Woker, 1948	3
Danio rerio	NR-ZERO	MOR	10,000	FW	24	h	-	-	Cairns *et al*, 1965	2
Danio rerio	NR-ZERO	MOR	10,000	FW	48	h	-	-	Cairns *et al*, 1965	2
Ptychocheilus oregonensis	-	MOR	10,000	FW	-	-	S	-	MacPhee and Ruelle, 1969	3

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration [a] (µg CN^-/l)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Ptychocheilus oregonensis	-	MOR	10,000	FW	-	-	S	-	MacPhee and Ruelle, 1969	3
Ptychocheilus oregonensis	-	MOR	10,000	FW	-	-	S	-	MacPhee and Ruelle, 1969	3
Danio rerio	LC_{50}	MOR	~ 11,700	FW	48	h	-	24	Cairns *et al*, 1965	2
Danio rerio	NR-LETH	MOR	18,000	FW	48	h	-	-	Cairns *et al*, 1965	2
Danio rerio	NR-LETH	MOR	18,000	FW	24	h	-	-	Cairns *et al*, 1965	2
Barbus holubi	-	PHY	10	FW	24	h	F	-	Morgan, 1976	4
Barbus holubi	-	PHY	10	FW	24	h	F	-	Morgan, 1977	4
Pimephales promelas	NOEC	REP	12.3	FW	256	d	F	25	Lind *et al*, 1977	2
Cyprinus carpio	NOEC	Survival	73	FW	42	d	F	20	Jee and Kang, 1999	4
Cyprinodontidae										
Jordanella floridae	NOEC	DVP	63	FW	140	h	F	25	Cheng and Ruby, 1981	2
Jordanella floridae	NOEC	DVP	< 63	FW	140	h	F	25	Cheng and Ruby, 1981	2
Jordanella floridae	-	DVP	72	FW	144	h	F	25	Cheng and Ruby, 1981	2
Jordanella floridae	NOEC	HIS	< 63	FW	-	-	F	25	Cheng and Ruby, 1981	2
Cyprinodontidae	-	MOR	370	FW	24	h	S	-	Schaut, 1939	4
Cyprinodontidae	NR-LETH	MOR	420	FW	24	h	S	-	Schaut, 1939	4
Jordanella floridae	NOEC	MPH	< 63	FW	-	-	F	25	Cheng and Ruby, 1981	3

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration [a] (µg CN^-/l)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Jordanella floridae	NOEC	MPH	< 63	FW	-	-	F	25	Cheng and Ruby, 1981	2
Jordanella floridae	NOEC	REP	< 63	FW	-	-	F	25	Cheng and Ruby, 1981	2
Jordanella floridae	NOEC	REP	< 63	FW	-	-	F	25	Cheng and Ruby, 1981	3
Jordanella floridae	NOEC	REP	< 63	FW	8	d	P	25	Cheng and Ruby, 1981	2
Jordanella floridae	NOEC	REP	< 63	FW	-	-	F	25	Cheng and Ruby, 1981	§
Jordanella floridae	NOEC	REP	< 63	FW	70	d	P	25	Cheng and Ruby, 1981	3
Cyrinidae										
Rasbora heteromorpha	LT_{50}	MOR	80	FW	-	-	-	-	Department of Scientific and Industrial Research, 1953	4
Rasbora heteromorpha	LT_{50}	MOR	200	FW	-	-	-	-	Department of Scientific and Industrial Research, 1953	4
Rasbora heteromorpha	LT_{50}	MOR	400	FW	~ 10	min	-	18	Department of Scientific and Industrial Research, 1953	4
Eleotridae										
Mogurnda mogurnda	NR-ZERO	MOR	≥ 200	FW	96	h	S	30	Rippon *et al*, 1992	2
Gasterosteidae										
Gasterosteus aculeatus	-	AVO	130	FW	-	-	S	-	Costa, 1965c	3
Gasterosteus aculeatus	-	AVO	260	FW	-	-	S	-	Costa, 1965c	3

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration [a] ($\mu g\ CN^-/l$)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Gasterosteus aculeatus	-	AVO	1,300	FW	0.042	h	S	-	Costa, 1965c	3
Gasterosteus aculeatus	-	AVO	1,300	FW	0.42	h	S	-	Costa, 1965c	3
Gasterosteus aculeatus	-	AVO	1,300	FW	0.28	h	S	-	Costa, 1965c	3
Gasterosteus aculeatus	-	AVO	1,300	FW	0.092	h	S	-	Costa, 1965c	3
Gasterosteus aculeatus	-	AVO	1,300	FW	0.092	h	S	-	Costa, 1965c	3
Gasterosteus aculeatus	-	AVO	1,300	FW	-	-	S	-	Costa, 1965c	3
Gasterosteus aculeatus	-	AVO	1,300	FW	0.33	h	S	-	Costa, 1965c	3
Gasterosteus aculeatus	-	AVO	1,300	FW	0.19	h	S	-	Costa, 1965c	3
Gasterosteus aculeatus	-	AVO	1,300	FW	0.075	h	S	-	Costa, 1965c	3
Gasterosteus aculeatus	LT_{50}	MOR	131	FW	13.73	h	S	-	Broderius, 1973	2
Gasterosteus aculeatus	LT_{50}	MOR	154	SW	8.4	h	S	-	Broderius, 1973	2
Gasterosteus aculeatus	LT_{50}	MOR	162	SW	10.83	h	S	-	Broderius, 1973	2
Gasterosteus aculeatus	LT_{50}	MOR	165	FW	10.7	h	S	-	Broderius, 1973	2
Gasterosteus aculeatus	LT_{50}	MOR	170	SW	9.7	h	S	-	Broderius, 1973	2
Gasterosteus aculeatus	LT_{50}	MOR	180.6	SW	5.83	h	S	-	Broderius, 1973	2
Gasterosteus aculeatus	LT_{50}	MOR	217	SW	6.18	h	S	-	Broderius, 1973	2
Gasterosteus aculeatus	LT_{50}	MOR	225	SW	3.3	h	S	-	Broderius, 1973	2

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration [a] (µg CN^-/l)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Gasterosteus aculeatus	LT_{50}	MOR	231	FW	6.87	h	S	-	Broderius, 1973	2
Gasterosteus aculeatus	-	MOR	1,300	FW	1.5	h	S	-	Costa, 1965c	3
Gasterosteus aculeatus	NR-LETH	MOR	2,600	FW	0.47	h	S	17	Jones, 1947	3
Gasterosteus aculeatus	NR-LETH	MOR	5,300	FW	0.33	h	S	17	Jones, 1947	3
Gasterosteus aculeatus	-	PHY	800	FW	2.58	h	S	17	Jones, 1947	3
Gobiidae										
Boleophthalmus boddarti	LC_{50}	MOR	279	SW	96	h	S	25	Chew and Ip, 1992	2
Boleophthalmus boddarti	LC_{50}	MOR	327	SW	48	h	S	25	Chew and Ip, 1992	2
Boleophthalmus boddarti	LC_{50}	MOR	356	SW	24	h	S	25	Chew and Ip, 1992	2
Ictaluridae										
Ameiurus melas	-	MOR	133	FW	72	h	-	24.4	Lewis and Tarrant, 1960	3
Ameiurus nebulosus	-	BCM	≥ 200	FW	7.75	h	F	-	Sawyer and Heath, 1988	3
Ictalurus natalis	LT_{100}	MOR	631	FW	9	h	S	24.4 - 26.7	Bridges, 1958	3
Ictalurus punctatus	LC_{50}	MOR	85.5	FW	26	h	F	25.2	Cardwell *et al*, 1976	2
Ictalurus punctatus	LC_{50}	MOR	88.2	FW	20	h	F	25.2	Cardwell *et al*, 1976	2
Ictalurus punctatus	LC_{50}	MOR	99.3	FW	10	h	F	25.2	Cardwell *et al*, 1976	2
Ictalurus punctatus	LC_{50}	MOR	132	FW	6	h	F	25.2	Cardwell *et al*, 1976	2

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration [a] (µg CN^-/l)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Ictalurus punctatus	LC_{50}	MOR	200	FW	24	h	S	5	Cairns *et al*, 1978	1
Ictalurus punctatus	LC_{50}	MOR	230	FW	24	h	S	30	Cairns *et al*, 1978	1
Ictalurus punctatus	LC_{50}	MOR	310	FW	24	h	S	15	Cairns *et al*, 1978	1
Kuhliidae										
Kuhlia sandvicensis	-	BEH	530	SW	0.033	h	S	-	Hiatt *et al*, 1953	3
Kuhlia sandvicensis	-	BEH	10,600	SW	0.033	h	S	-	Hiatt *et al*, 1953	3
Lepisosteidae										
Lepisosteus osseus	LT_{100}	MOR	531	-	4.2	h	S	22.8 - 23.3	Bridges, 1958	**3**
Melanotaeniidae										
Melanotaenia nigrans	LT_{50}	MOR	80	FW	-	-	-	-	Department of Scientific and Industrial	4
Melanotaenia nigrans	LT_{50}	MOR	200	FW	-	-	-	-	Department of Scientific and Industrial	4
Melanotaenia nigrans	LT_{50}	MOR	400	FW	-	-	-	-	Department of Scientific and Industrial	4
Mormyridae										
Gnathonemus tamandua	NOEC	PHY	< 5	FW	-	-	F	25	Lewis *et al*, 1992	3
Gnathonemus petersi	NOEC	PHY	< 5	FW	-	-	F	25	Lewis *et al*, 1992	3
Gnathonemus petersi	-	PHY	100	FW	4	h	F	25 - 27	Geller, 1984	3

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration [a] (µg CN^-/l)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Mugildae										
Mugil auratus	-	BCM	159	SW	24	h	F	-	Ozretic and Krajnovic-Ozretic, 1993	3
Mugil auratus	-	BCM	159	SW	24	h	F	-	Ozretic and Krajnovic-Ozretic, 1993	3
Mugil auratus	-	ENZ	159	SW	24	h	F	-	Ozretic and Krajnovic-Ozretic, 1993	3
Percidae										
Perca flavescens	LC_{50}	MOR	73	FW	96	h	F	21	Smith *et al*, 1978	2
Perca flavescens	LC_{50}	MOR	87.1	FW	96	h	F	15	Smith *et al*, 1978	2
Perca flavescens	LC_{50}	MOR	90.5	FW	96	h	F	18	Smith *et al*, 1978	2
Perca flavescens	LC_{50}	MOR	92.4	FW	96	h	F	21	Smith *et al*, 1978	2
Perca fluviatilis	LC_{50}	MOR	96	FW	24	h	F	11 - 12.5	Solbé *et al*, 1985	2
Perca flavescens	LC_{50}	MOR	98.2	FW	96	h	F	21	Smith *et al*, 1978	2
Perca flavescens	LC_{50}	MOR	104	FW	96	h	F	21	Smith *et al*, 1978	2
Perca flavescens	LC_{50}	MOR	> 266	FW	96	h	F	18	Smith *et al*, 1978	3
Perca flavescens	LC_{50}	MOR	277	FW	96	h	F	14	Smith *et al*, 1978	2
Perca flavescens	LC_{50}	MOR	284	FW	96	h	F	14	Smith *et al*, 1978	2
Perca flavescens	LC_{50}	MOR	> 305	FW	96	h	F	14	Smith *et al*, 1978	3
Perca flavescens	LC_{50}	MOR	> 317	FW	96	h	F	14	Smith *et al*, 1978	3

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration [a] (µg CN^-/l)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Perca flavescens	LC_{50}	MOR	325	FW	96	h	F	14	Smith *et al*, 1978	2
Perca flavescens	LC_{50}	MOR	> 325	FW	96	h	F	18	Smith *et al*, 1978	3
Perca flavescens	LC_{50}	MOR	> 344	FW	96	h	F	10	Smith *et al*, 1978	3
Perca flavescens	LC_{50}	MOR	> 375	FW	96	h	F	14	Smith *et al*, 1978	3
Perca flavescens	LC_{50}	MOR	> 380	FW	96	h	F	14	Smith *et al*, 1978	3
Petromyzontidae										
Petromyzon marinus	-	BEH	5,000	FW	2	h	S	-	Applegate *et al*, 1957	4
Pleuronectidae										
Pseudopleuronectes americanus	LC_{50}	MOR	372	SW	96	h	-	-	Brix *et al*, 2000	2
Poeciliidae										
Poecilia reticulata	LT_{50}	MOR	80	FW	-	-	-	-	Department of Scientific and Industrial Research, 1953	4
Poecilia reticulata	NR-ZERO	MOR	84	FW	5	d	F	25	Chen and Selleck, 1969	3
Poecilia reticulata	LT_{50}	MOR	200	FW	-	-	-	-	Department of Scientific and Industrial Research, 1953	4
Poecilia reticulata	LD_{50}	MOR	284	-	1.5	h	-	-	Nagasawa *et al*, 1968	4
Poecilia reticulata	LD_{50}	MOR	307	-	2.8	h	-	-	Nagasawa *et al*, 1968	4

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration [a] (µg CN^-/l)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Poecilia reticulata	LT_{50}	MOR	400	FW	-	-	-	-	Department of Scientific and Industrial Research, 1953	4
Gambusia affinis	LC_{50}*	MOR	640	FW	96	h	S	21 - 23	Wallen *et al*, 1957	2
Gambusia affinis	LC_{50}*	MOR	640	FW	24	h	S	21 - 23	Wallen *et al*, 1957	2
Gambusia affinis	LC_{50}*	MOR	640	FW	48	h	S	21 - 23	Wallen *et al*, 1957	2
Gambusia affinis	LC_{50}	MOR	792	FW	96	h	S	-	Mowbray, 1988	4
Poecilia reticulata	LC_{50}	MOR	800	FW	96	h	-	20	Tscheu-Schlüter and Skibba, 1986	2
Poecilia reticulata	LC_{50}	MOR	800	-	24	h	S	20	Tscheu-Schlüter, 1983	2
Pomacentridae										
Pomacentrus coelestis	-	HIS	5,311	SW	16	d	-	24.2	Hall and Bellwood, 1995	2
Pomacentrus coelestis	-	MOR	5,311	SW	-	-	S	24.2	Hall and Bellwood, 1995	2
Salmonidae										
Oncorhynchus mykiss	RPI_{50}		10	FW	-	-	F	-	Leduc, 1977	2
Oncorhynchus mykiss	-	~ PHY	28	FW	24	h	F	10	Carballo *et al*, 1995	3
Oncorhynchus mykiss	-	~ PHY	50	FW	21	d	S	15	Carballo and Muñoz, 1991	3
Oncorhynchus mykiss	BCF	ACC	9.6	FW	15	d	-	-	Bois and Leduc, 1988	4
Oncorhynchus mykiss	BCF	ACC	9.6	FW	15	d	-	-	Bois and Leduc, 1988	4

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration [a] (µg CN^-/l)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Oncorhynchus mykiss	BCF	ACC	19.3	FW	15	d	-	-	Bois and Leduc, 1988	4
Oncorhynchus mykiss	BCF	ACC	19.3	FW	15	d	-	-	Bois and Leduc, 1988	4
Salmo trutta	-	AVO	260	FW	-	-	S	-	Costa, 1965c	3
Salmo trutta	-	AVO	1,300	FW	-	-	S	-	Costa, 1965c	3
Salmo trutta	-	AVO	1,300	FW	-	-	S	-	Costa, 1965c	3
Oncorhynchus mykiss	LOEC	BCM	4.8	FW	20	d	F	-	Kovacs, 1979	3
Oncorhynchus mykiss	NOEC	BCM	4.8	FW	20	d	F	6	Kovacs, 1979	3
Oncorhynchus mykiss	-	BCM	5.2	FW	-	-	R	-	Carballo, 1992	4
Oncorhynchus mykiss	-	BCM	9.6	FW	7	d	F	12.5	Da Costa and Ruby, 1984	3
Oncorhynchus mykiss	NOEC	BCM	< 9.6	FW	20	d	F	12	Kovacs, 1979	3
Oncorhynchus mykiss	LOEC	BCM	9.6	FW	20	d	F	-	Kovacs, 1979	3
Oncorhynchus mykiss	NOEC	BCM	≤ 10	FW	12	d	F	1.5	Szabo *et al*, 1991	2
Oncorhynchus mykiss	-	BCM	14.5	FW	20	d	F	-	Kovacs, 1979	3
Oncorhynchus mykiss	-	BCM	19.3	FW	7	d	F	-	Da Costa and Ruby, 1984	3
Oncorhynchus mykiss	-	BCM	19.3	FW	21	d	F	-	Speyer, 1975	4
Oncorhynchus mykiss	-	BCM	≥ 20	FW	8.5	h	F	-	Sawyer and Heath, 1988	3
Oncorhynchus mykiss	-	BCM	20.8	FW	21	d	S	10	Muñoz *et al*, 1991	3

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration [a] (µg CN^-/l)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Oncorhynchus mykiss	NOEC	BCM	24.1	FW	20	d	F	18	Kovacs, 1979	3
Oncorhynchus mykiss	-	BCM	70	FW	24	h	F	-	Carballo *et al*, 1995	3
Oncorhynchus mykiss	-	BEH	19.3	FW	21	d	F	-	Speyer, 1975	4
Salvelinus fontinalis	-	BEH	500	FW	0.05	h	S	-	Wuhrmann and Woker, 1953	3
Salvelinus fontinalis	-	BEH	530	FW	0.08	h	S	-	Wuhrmann and Woker, 1953	3
Salvelinus fontinalis	-	BEH	560	FW	0.07	h	S	-	Wuhrmann and Woker, 1953	3
Salvelinus fontinalis	-	BEH	570	FW	0.2	h	S	-	Wuhrmann and Woker, 1953	3
Salvelinus fontinalis	-	BEH	620	FW	0.12	h	S	-	Wuhrmann and Woker, 1953	3
Salvelinus fontinalis	-	BEH	650	FW	0.03	h	S	-	Wuhrmann and Woker, 1953	3
Oncorhynchus mykiss	-	BEH	5,000	FW	2	h	S	-	Applegate *et al*, 1957	4
Oncorhynchus tshawytscha	-	BEH	10,000	FW	-	-	S	-	MacPhee and Ruelle, 1969	3
Oncorhynchus kisutch	-	BEH	10,000	FW	-	-	S	-	MacPhee and Ruelle, 1969	3
Salmo salar	-	DVP	10	FW	170	d	F	-	Leduc, 1978	3
Salvelinus fontinalis	-	DVP	11.3	FW	30	d	F	-	Koenst *et al*, 1977	3
Oncorhynchus mykiss	-	ENZ	9	FW	24	h	F	-	Raymond *et al*, 1986	4
Oncorhynchus mykiss	-	FDB	19.26	FW	21	d	F	-	Speyer, 1975	4
Oncorhynchus mykiss	NOEC	GRO	< 4.8	FW	20	d	F	6	Kovacs and Leduc, 1982b	3

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration [a] (µg CN^-/l)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Oncorhynchus mykiss	NOEC	GRO	4.8	FW	20	d	F	6	Kovacs and Leduc, 1982b	3
Oncorhynchus mykiss	LOEC	GRO	4.8	FW	20	d	F	-	Kovacs, 1979	3
Oncorhynchus mykiss	NOEC	GRO	4.8	FW	20	d	F	6	Kovacs, 1979	2
Oncorhynchus mykiss	-	GRO	9.6	FW	12	d	F	-	Ruby *et al*, 1993a	3
Oncorhynchus mykiss	NOEC	GRO	< 9.6	FW	20	d	F	10	McCracken and Leduc, 1980	2
Oncorhynchus mykiss	NOEC	GRO	9.6	FW	20	d	F	6	Kovacs, 1979	2
Oncorhynchus mykiss	NOEC	GRO	≤ 9.6	FW	12	d	F	-	Ruby *et al*, 1993b	2
Oncorhynchus mykiss	NOEC	GRO	9.6	FW	20	d	F	6	Kovacs and Leduc, 1982b	3
Oncorhynchus mykiss	LOEC	GRO	9.6	FW	20	d	F	6	Kovacs, 1979	2
Oncorhynchus tshawytscha	-	GRO	10	FW	2	month	F	-	Negilski, 1973	4
Salvelinus fontinalis	NOEC	GRO	10.6	FW	30	d	F	-	Koenst *et al*, 1977	2
Salvelinus fontinalis	-	GRO	11.3	FW	90	d	F	-	Koenst *et al*, 1977	3
Oncorhynchus mykiss	NOEC	GRO	≥ 12.5	FW	20	d	F	10	McCracken and Leduc, 1980	3
Oncorhynchus mykiss	LOEC	GRO	14.5	FW	20	d	F	6	Kovacs, 1979	2
Oncorhynchus mykiss	-	GRO	193	FW	-	-	F	-	Speyer, 1975	4
Oncorhynchus mykiss	NOEC	GRO	19.3	FW	20	d	F	12	Kovacs and Leduc, 1982b	3
Oncorhynchus mykiss	NOEC	GRO	19.3	FW	20	d	F	12	Kovacs, 1979	2

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration[a] ($\mu g\ CN^-/l$)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Salmo salar	-	GRO	20	FW	170	d	F	-	Leduc, 1978	3
Salvelinus fontinalis	-	GRO	20.9	FW	60	d	F	-	Koenst *et al*, 1977	2
Salvelinus fontinalis	-	GRO	21.8	FW	90	d	F	-	Koenst *et al*, 1977	3
Oncorhynchus mykiss	LOEC	GRO	28.9	FW	20	d	F	12	Kovacs, 1979	2
Oncorhynchus mykiss	NOEC	GRO	28.9	FW	20	d	F	18	Kovacs, 1979	2
Oncorhynchus mykiss	NOEC	GRO	28.9	FW	20	d	F	18	Kovacs and Leduc, 1982b	3
Salvelinus fontinalis	-	GRO	32.1	FW	90	d	F	-	Koenst *et al*, 1977	2
Salvelinus fontinalis	-	GRO	33.3	FW	90	d	F	-	Koenst *et al*, 1977	3
Salvelinus fontinalis	-	GRO	33.3	FW	60	d	F	-	Koenst *et al*, 1977	3
Salmo salar	-	GRO	40	FW	170	d	F	-	Leduc, 1978	3
Oncorhynchus mykiss	LOEC	GRO	43.3	FW	20	d	F	18	Kovacs, 1979	2
Oncorhynchus mykiss	-	GRO	45	FW	20	d	F	-	Kovacs and Leduc, 1982b	3
Salvelinus fontinalis	NOEC	GRO	≥ 72.5	FW	144	d	F	-	Koenst *et al*, 1977	2
Oncorhynchus mykiss	NOEC	HIS	< 9.6	FW	20	d	F	10	Lesniak and Ruby, 1982	2
Oncorhynchus mykiss	NOEC	HIS	≤ 9.6	FW	12	d	F	-	Ruby *et al*, 1993a	2
Oncorhynchus mykiss	EC_{50}	HIS	9.6	FW	18	d	F	12.5	Ruby *et al*, 1979	2
Oncorhynchus mykiss	NOEC	HIS	9.6	FW	12	d	F	-	Ruby *et al*, 1993b	2

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration[a] (µg CN^-/l)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Oncorhynchus mykiss	-	HIS	9.6	FW	18	d	F	12.5	Ruby *et al*, 1979	2
Oncorhynchus mykiss	-	HIS	19.3	FW	15	d	-	-	Bois and Leduc, 1988	4
Oncorhynchus mykiss	EC_{50}	HRM	9.6	FW	12	d	F	-	Ruby *et al*, 1993b	2
Oncorhynchus mykiss	NR-ZERO	MOR	9.6	FW	20	d	F	6	Kovacs, 1979	3
Salmo salar	-	MOR	10	FW	170	d	F	-	Leduc, 1978	3
Salmo salar	-	MOR	10	FW	170	d	F	-	Leduc, 1978	3
Oncorhynchus mykiss	-	MOR	14.5	FW	20	d	F	-	Kovacs, 1979	3
Oncorhynchus mykiss	-	MOR	15	FW	20	d	F	-	Kovacs and Leduc, 1982a	3
Oncorhynchus mykiss	NR-ZERO	MOR	17.3	FW	96	h	F	6	Kovacs, 1979	2
Oncorhynchus mykiss	-	MOR	19.3	FW	21	d	F	-	Speyer, 1975	4
Salmo salar	-	MOR	20	FW	170	d	F	-	Leduc, 1978	3
Salvelinus fontinalis	NR-LETH	MOR	20	FW	> 650	h	F	-	Karsten, 1934	3
Salmo salar	LC_{50}	MOR	23	FW	24	h	F	11	Alabaster *et al*, 1983	2
Oncorhynchus mykiss	NR-ZERO	MOR	24	FW	96	h	S	12	Monsanto, 1981b	1
Oncorhynchus mykiss	LC_{50}	MOR	27.0	FW	96	h	F	6	Kovacs, 1979	3
Oncorhynchus mykiss	LC_{50}	MOR	27.0	FW	96	h	F	6	Kovacs and Leduc, 1982a	2
Oncorhynchus mykiss	NR-ZERO	MOR	28.9	FW	20	d	F	-	Kovacs, 1979	3

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration[a] ($\mu g\ CN^-/l$)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Oncorhynchus mykiss	NR-ZERO	MOR	28.9	FW	20	d	F	18	Kovacs, 1979	3
Oncorhynchus mykiss	-	MOR	30	FW	20	d	F	-	Kovacs and Leduc, 1982a	3
Oncorhynchus mykiss	NR-ZERO	MOR	30.8	FW	96	h	F	18	Kovacs, 1979	2
Oncorhynchus mykiss	LT_{50}	MOR	40	FW	> 24	h	S	10 - 11	Shaw, 1979	3
Salmo salar	-	MOR	40	FW	170	d	F	-	Leduc, 1978	3
Oncorhynchus mykiss	LC_{50}	MOR	40.5	FW	96	h	F	12	Kovacs, 1979	3
Oncorhynchus mykiss	LC_{50}	MOR	40.5	FW	96	h	F	12	Kovacs and Leduc, 1982a	2
Oncorhynchus mykiss	LC_{50}	MOR	41	FW	96	h	F	12	McGeachy and Leduc, 1988	2
Salvelinus fontinalis	NOEC	MOR	42	FW	90	d	F	9 - 15	Koenst *et al*, 1977	2
Oncorhynchus mykiss	-	MOR	42	FW	30	d	F	10	Broderius and Smith, 1979	3
Oncorhynchus mykiss	-	MOR	43.3	FW	20	d	F	-	Kovacs, 1979	3
Oncorhynchus mykiss	-	MOR	45	FW	20	d	F	-	Kovacs and Leduc, 1982a	3
Oncorhynchus mykiss	LC_{50}	MOR	46.3	FW	96	h	S	12	Marking *et al*, 1984	2
Salvelinus fontinalis	NR-LETH	MOR	50	FW	130	h	F	-	Karsten, 1934	3
Salvelinus fontinalis	NR-LETH	MOR	50	FW	136	h	F	-	Karsten, 1934	3

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration [a] (µg CN^-/l)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Salvelinus fontinalis	NR-ZERO	MOR	50	FW	≥ 40	d	F	9	Neil, 1957	2
Salvelinus fontinalis	LC_{50}	MOR	51.04	FW	96	h	F	4	Smith *et al*, 1978	2
Oncorhynchus mykiss	NR-LETH	MOR	51.0	FW	96	h	F	12	Kovacs, 1979	3
Oncorhynchus mykiss	LC_{50}	MOR	52.1	FW	96	h	S	12	Marking *et al*, 1984	2
Oncorhynchus mykiss	LC_{50}	MOR	53	FW	96	h	F	12	McGeachy and Leduc, 1988	2
Salvelinus fontinalis	LC_{50}	MOR	53.7	FW	96	h	F	10	Smith *et al*, 1978	2
Oncorhynchus mykiss	LC_{50}	MOR	54.1	FW	96	h	S	12	Marking *et al*, 1984	2
Oncorhynchus mykiss	LC_{50}	MOR	55	FW	96	h	F	10	Broderius and Smith, 1979	2
Oncorhynchus mykiss	LC_{50}	MOR	55.1	FW	96	h	F	-	Smith *et al*, 1978	3
Salvelinus fontinalis	-	MOR	55.3	FW	90	d	F	-	Koenst *et al*, 1977	3
Oncorhynchus mykiss	NR-ZERO	MOR	57.8	FW	96	h	F	12	Kovacs, 1979	2
Salvelinus fontinalis	LC_{50}	MOR	59.5	FW	96	h	F	6	Smith *et al*, 1978	2
Oncorhynchus mykiss	LT_{50}	MOR	59.8	FW	74	h	F	17.5	Herbert and Merkens, 1952	2
Oncorhynchus mykiss	NR-ZERO	MOR	60	FW	96	h	-	-	Skibba, 1981	2
Oncorhynchus mykiss	LC_{50}	MOR	60	FW	96	h	S	-	Qureshi *et al*, 1982	4
Oncorhynchus mykiss	LC_{50}	MOR	62.1	FW	96	h	S	12	Marking *et al*, 1984	2
Oncorhynchus mykiss	LC_{50}	MOR	65.5	FW	96	h	F	18	Kovacs and Leduc, 1982a	2

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration[a] ($\mu g\ CN^-/l$)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Oncorhynchus mykiss	LC_{50}	MOR	65.5	FW	96	h	F	18	Kovacs, 1979	3
Salvelinus fontinalis	LC_{50}	MOR	65.8	FW	96	h	F	9	Smith *et al*, 1978	2
Salvelinus fontinalis	LC_{50}	MOR	65.9	FW	264	h	F	15.4	Cardwell *et al*, 1976	2
Salvelinus fontinalis	LC_{50}	MOR	66.9	FW	288	h	F	15.4	Cardwell *et al*, 1976	2
Oncorhynchus mykiss	LC_{50}	MOR	67	FW	96	h	S	12	Monsanto, 1981b	1
Oncorhynchus mykiss	LC_{50}	MOR	67.4	FW	48	h	-	15	Brown, 1968	3
Salvelinus fontinalis	LC_{50}	MOR	67.5	FW	264	h	F	15.4	Cardwell *et al*, 1976	2
Salvelinus fontinalis	LC_{50}	MOR	69.6	FW	240	h	F	15.4	Cardwell *et al*, 1976	2
Salvelinus fontinalis	LC_{50}	MOR	69.8	FW	96	h	F	12	Smith *et al*, 1978	2
Salmo salar	LC_{50}	MOR	70	FW	24	h	F	11	Alabaster *et al*, 1983	2
Salvelinus fontinalis	LC_{50}	MOR	70.6	FW	264	h	F	15.4	Cardwell *et al*, 1976	2
Salvelinus fontinalis	NOEC	MOR	$\geq$ 72.5	FW	144	d	F	9 - 15	Koenst *et al*, 1977	2
Salvelinus fontinalis	LC_{50}	MOR	72.6	FW	96	h	F	7	Smith *et al*, 1978	2
Oncorhynchus mykiss	LC_{50}	MOR	73	FW	96	h	F	18	McGeachy and Leduc, 1988	2
Salvelinus fontinalis	LC_{50}	MOR	74.1	FW	96	h	F	10	Smith *et al*, 1978	2
Oncorhynchus mykiss	LC_{50}	MOR	74.8	FW	96	h	S	12	Marking *et al*, 1984	2
Salvelinus fontinalis	LC_{50}	MOR	74.9	FW	240	h	F	15.4	Cardwell *et al*, 1976	2

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration[a] ($\mu g\ CN^-/l$)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Oncorhynchus mykiss	LC_{50}*	MOR	75	FW	96	h	S	-	Goode *et al*, 1976	4
Salvelinus fontinalis	-	MOR	77.2	FW	90	d	F	-	Koenst *et al*, 1977	3
Oncorhynchus mykiss	LC_{50}	MOR	78.6	FW	96	h	S	-	Office of Pesticide Programs, 2000	4
Salmo salar	-	MOR	80	FW	170	d	F	-	Leduc, 1978	3
Oncorhynchus mykiss	LT_{50}	MOR	80	FW	-	-	-	-	Department of Scientific and Industrial Research, 1953	4
Salvelinus fontinalis	LC_{50}	MOR	80.7	FW	168	h	F	15.4	Cardwell *et al*, 1976	2
Salvelinus fontinalis	LC_{50}	MOR	81.3	FW	96	h	F	7	Smith *et al*, 1978	2
Oncorhynchus mykiss	LC10	MOR	82	FW	96	h	-	20	Tscheu-Schlüter and Skibba, 1986	2
Salvelinus fontinalis	LC_{50}	MOR	82.8	FW	96	h	F	7	Smith *et al*, 1978	2
Salvelinus fontinalis	LC_{50}	MOR	82.9	FW	96	h	F	15.4	Cardwell *et al*, 1976	2
Oncorhynchus mykiss	NR-LETH	MOR	83.8	FW	96	h	F	18	Kovacs, 1979	3
Salvelinus fontinalis	LC_{50}	MOR	83.9	FW	21	h	F	15.4	Cardwell *et al*, 1976	2
Salvelinus fontinalis	LC_{50}	MOR	85.1	FW	96	h	F	10	Smith *et al*, 1978	2
Salvelinus fontinalis	LC_{50}	MOR	85.3	FW	96	h	F	10	Smith *et al*, 1978	2
Oncorhynchus mykiss	LC_{50}	MOR	86	FW	24	h	S	12	Monsanto, 1981b	1
Salvelinus fontinalis	LC_{50}	MOR	86.6	FW	48	h	F	15.4	Cardwell *et al*, 1976	2

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration[a] ($\mu g\ CN^-/l$)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Salvelinus fontinalis	LC_{50}	MOR	88.8	FW	96	h	F	13	Smith *et al*, 1978	2
Oncorhynchus mykiss	LC_{50}	MOR	90	FW	96	h	S	-	Bills *et al*, 1977	4
Oncorhynchus mykiss	LC_{50}	MOR	90	FW	24	h	S	5	Cairns *et al*, 1978	1
Salvelinus fontinalis	LC_{50}	MOR	90	FW	96	h	F	10	Smith *et al*, 1978	2
Salvelinus fontinalis	LC_{50}	MOR	90	FW	10	h	F	15.4	Cardwell *et al*, 1976	2
Oncorhynchus mykiss	LC_{50}	MOR	92	FW	24	h	S	30	Cairns *et al*, 1978	1
Salvelinus fontinalis	LC_{50}	MOR	93.9	FW	96	h	F	15	Smith *et al*, 1978	2
Salvelinus fontinalis	LC_{50}	MOR	94.9	FW	96	h	F	13	Smith *et al*, 1978	2
Salvelinus fontinalis	LC_{50}	MOR	96.3	FW	96	h	F	10	Smith *et al*, 1978	2
Oncorhynchus mykiss	LC_{50}	MOR	97	FW	96	h	-	21	Skibba, 1981	2
Oncorhynchus mykiss	LC_{50}	MOR	97	FW	96	h	-	20	Tscheu-Schlüter and Skibba, 1986	2
Oncorhynchus mykiss	LC_{50}	MOR	98	FW	24	h	S	15	Cairns *et al*, 1978	1
Oncorhynchus mykiss	LC_{50}	MOR	98	FW	6	d	F	-	Dixon and Sprague, 1981	4
Salmo salar	-	MOR	100	FW	170	d	F	-	Leduc, 1978	3
Salvelinus fontinalis	LC_{50}	MOR	102	FW	96	h	F	10	Smith *et al*, 1978	2
Salvelinus fontinalis	LC_{50}	MOR	104	FW	96	h	F	10	Smith *et al*, 1978	2
Salvelinus fontinalis	LC_{50}	MOR	104	FW	24	h	F	15.4	Cardwell *et al*, 1976	2

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration[a] ($\mu g\ CN^-/l$)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Salvelinus fontinalis	LC_{50}	MOR	108	FW	96	h	F	13	Smith *et al*, 1978	2
Salvelinus fontinalis	LC_{50}	MOR	112	FW	12	h	F	15.4	Cardwell *et al*, 1976	2
Salvelinus fontinalis	LC_{50}	MOR	118	FW	7	h	F	15.4	Cardwell *et al*, 1976	2
Oncorhynchus mykiss	LT_{50}	MOR	120	FW	7.13	h	S	10 - 11	Shaw, 1979	3
Oncorhynchus mykiss	NR-LETH	MOR	120	FW	24	h	-	-	Skibba, 1981	2
Salvelinus fontinalis	LC_{50}	MOR	138	FW	96	h	F	18	Smith *et al*, 1978	2
Salvelinus fontinalis	LC_{50}	MOR	138	FW	6	h	F	15.4	Cardwell *et al*, 1976	2
Oncorhynchus mykiss	LT_{50}	MOR	149	FW	0.78	h	F	17.5	Herbert and Merkens, 1952	2
Oncorhynchus mykiss	LT_{50}	MOR	149	FW	0.59	h	F	17.5	Herbert and Merkens, 1952	2
Oncorhynchus mykiss	LT_{50}	MOR	150	FW	0.85	h	F	17.5	Herbert and Merkens, 1952	2
Oncorhynchus mykiss	LT_{50}	MOR	150	FW	0.66	h	F	17.5	Herbert and Merkens, 1952	2
Oncorhynchus mykiss	LT_{50}	MOR	151	FW	0.48	h	F	17.5	Herbert and Merkens, 1952	2
Oncorhynchus mykiss	LT_{50}	MOR	153	FW	0.37	h	F	17.5	Herbert and Merkens, 1952	2
Oncorhynchus mykiss	LT_{50}	MOR	153	FW	0.4	h	F	17.5	Herbert and Merkens, 1952	2
Oncorhynchus mykiss	LT_{50}	MOR	153	FW	0.62	h	F	17.5	Herbert and Merkens, 1952	2
Oncorhynchus mykiss	LT_{50}	MOR	153	FW	0.2	h	F	17.5	Herbert and Merkens, 1952	2
Oncorhynchus mykiss	LT_{50}	MOR	153	FW	0.47	h	F	17.5	Herbert and Merkens, 1952	2

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration[a] ($\mu g\ CN^-/l$)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Oncorhynchus mykiss	LT_{50}	MOR	153	FW	0.31	h	F	17.5	Herbert and Merkens, 1952	2
Oncorhynchus mykiss	LT_{50}	MOR	153	FW	0.28	h	F	17.5	Herbert and Merkens, 1952	2
Oncorhynchus mykiss	LT_{50}	MOR	153	FW	0.27	h	F	17.5	Herbert and Merkens, 1952	2
Oncorhynchus mykiss	LT_{50}	MOR	153	FW	0.65	h	F	17.5	Herbert and Merkens, 1952	2
Oncorhynchus mykiss	LT_{50}	MOR	153	FW	0.56	h	F	17.5	Herbert and Merkens, 1952	2
Oncorhynchus mykiss	LT_{50}	MOR	197	FW	0.044	h	F	17.5	Herbert and Merkens, 1952	2
Oncorhynchus mykiss	LT_{50}	MOR	200	FW	1.52	h	S	10 - 11	Shaw, 1979	3
Oncorhynchus mykiss	LT_{50}	MOR	200	FW	-	-	-	-	Department of Scientific and Industrial Research, 1953	4
Salvelinus fontinalis	LC_{50}	MOR	> 204	FW	96	h	F	7	Smith *et al*, 1978	3
Salvelinus fontinalis	NR-LETH	MOR	217	FW	210	min	F	-	Karsten, 1934	3
Salmo trutta levensis	NR-LETH	MOR	217	FW	140	min	F	-	Karsten, 1934	3
Salvelinus fontinalis	LC_{50}	MOR	> 220	FW	96	h	F	10	Smith *et al*, 1978	3
Salvelinus fontinalis	LC_{50}	MOR	> 223	FW	96	h	F	13	Smith *et al*, 1978	3
Salvelinus fontinalis	LC_{50}	MOR	> 223	FW	96	h	F	10	Smith *et al*, 1978	3
Salvelinus fontinalis	LC_{50}	MOR	> 233	FW	96	h	F	10	Smith *et al*, 1978	3
Salvelinus fontinalis	LC_{50}	MOR	247	FW	96	h	F	13	Smith *et al*, 1978	2

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration[a] (µg CN^-/l)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Salmo trutta	LT_{50}	MOR	320	FW	1.1	h	F	-	Burdick *et al*, 1958	3
Salvelinus fontinalis	LC_{50}	MOR	337	FW	96	h	F	10	Smith *et al*, 1978	2
Oncorhynchus mykiss	NR-LETH	MOR	356	FW	96	h	F	6	Kovacs, 1979	3
Salvelinus fontinalis	NR-LETH	MOR	392	FW	58	min	F	-	Karsten, 1934	3
Oncorhynchus mykiss	LT_{50}	MOR	400	FW	1.08	h	S	10 - 11	Shaw, 1979	3
Oncorhynchus mykiss	LT_{50}	MOR	400	FW	~ 10	min	-	-	Department of Scientific and Industrial Research, 1953	4
Oncorhynchus mykiss	NR-LETH	MOR	400	FW	1	h	R	7	Van Hoof, 1980	3
Salvelinus fontinalis	LC_{50}	MOR	499	FW	96	h	F	10	Smith *et al*, 1978	2
Oncorhynchus mykiss	LT_{50}	MOR	600	FW	0.88	h	S	10 - 11	Shaw, 1979	3
Salvelinus fontinalis	NR-LETH	MOR	784	FW	35	min	F	-	Karsten, 1934	3
Salvelinus fontinalis	NR-LETH	MOR	853	FW	26	min	F	-	Karsten, 1934	3
Oncorhynchus mykiss	NR-LETH	MOR	1,600	FW	1.25	h	R	7	Van Hoof, 1980	2
Salvelinus fontinalis	NR-LETH	MOR	1,710	FW	12.7	min	F	-	Karsten, 1934	3
Salvelinus fontinalis	NR-LETH	MOR	1,870	FW	11.9	min	F	-	Karsten, 1934	3
Oncorhynchus mykiss	LT_{50}	MOR	2,000	FW	0.57	h	S	10 - 11	Shaw, 1979	3
Salmo trutta levensis	NR-LETH	MOR	2,070	FW	8.2	min	F	-	Karsten, 1934	3

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration[a] ($\mu g\ CN^-/l$)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Salmo trutta levensis	NR-LETH	MOR	2,100	FW	8.9	min	F	-	Karsten, 1934	3
Salvelinus fontinalis	NR-LETH	MOR	2,130	FW	11.7	min	F	-	Karsten, 1934	3
Salmo trutta levensis	-	MOR	3,200	FW	27	min	F	-	Karsten, 1934	3
Salmo trutta levensis	-	MOR	3,200	FW	-	-	-	-	Karsten, 1934	3
Salvelinus fontinalis	NR-LETH	MOR	4,140	FW	11.1	min	F	-	Karsten, 1934	3
Salmo trutta levensis	NR-LETH	MOR	4,140	FW	8.9	min	F	-	Karsten, 1934	3
Salvelinus fontinalis	NR-LETH	MOR	4,290	FW	10.8	min	F	-	Karsten, 1934	3
Salvelinus fontinalis	NR-LETH	MOR	4,450	FW	15	min	F	-	Karsten, 1934	3
Salmo trutta levensis	NR-LETH	MOR	4,660	FW	9	min	F	-	Karsten, 1934	3
Salmo trutta levensis	NR-LETH	MOR	4,980	FW	9	min	F	-	Karsten, 1934	3
Salmo trutta levensis	NR-LETH	MOR	4,980	FW	8.1	min	F	-	Karsten, 1934	3
Salmo trutta levensis	NR-LETH	MOR	7,980	FW	10.4	min	F	-	Karsten, 1934	3
Salmo trutta levensis	NR-LETH	MOR	8,030	FW	8.2	min	F	-	Karsten, 1934	3
Salmo trutta levensis	NR-LETH	MOR	8,030	FW	10	min	F	-	Karsten, 1934	3
Salmo trutta levensis	NR-LETH	MOR	8,030	FW	10.1	min	F	-	Karsten, 1934	3
Salmo trutta levensis	NR-LETH	MOR	8,060	FW	8.6	min	F	-	Karsten, 1934	3
Salvelinus fontinalis	NR-LETH	MOR	8,060	FW	9.8	min	F	-	Karsten, 1934	3
Salvelinus fontinalis	NR-LETH	MOR	8,080	FW	9.2	min	F	-	Karsten, 1934	3

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration[a] ($\mu g\ CN^-/l$)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Salvelinus fontinalis	NR-LETH	MOR	8,120	FW	14.6	min	F	-	Karsten, 1934	3
Salmo trutta levensis	NR-LETH	MOR	8,180	FW	8.4	min	F	-	Karsten, 1934	3
Salvelinus fontinalis	NR-LETH	MOR	8,180	FW	10.1	min	F	-	Karsten, 1934	3
Salvelinus fontinalis	NR-LETH	MOR	8,190	FW	15.1	min	F	-	Karsten, 1934	3
Salvelinus fontinalis	NR-LETH	MOR	8,250	FW	14.7	min	F	-	Karsten, 1934	3
Salvelinus fontinalis	NR-LETH	MOR	8,640	FW	15.2	min	F	-	Karsten, 1934	3
Oncorhynchus tshawytscha	-	MOR	10,000	FW	-	-	S	-	MacPhee and Ruelle, 1969	3
Oncorhynchus tshawytscha	-	MOR	10,000	FW	-	-	S	-	MacPhee and Ruelle, 1969	3
Oncorhynchus tshawytscha	-	MOR	10,000	FW	-	-	S	-	MacPhee and Ruelle, 1969	3
Oncorhynchus kisutch	-	MOR	10,000	FW	-	-	S	-	MacPhee and Ruelle, 1969	3
Oncorhynchus kisutch	-	MOR	10,000	FW	-	-	S	-	MacPhee and Ruelle, 1969	3
Oncorhynchus kisutch	-	MOR	10,000	FW	-	-	S	-	MacPhee and Ruelle, 1969	3
Salmo salar	NOEC	PHY	≤ 4.8	FW	12	d	F	7	Ruby *et al*, 1987	2
Salmo salar	MATC	PHY	5	FW	170	d	F	1.5 - 11	Leduc, 1978	2
Oncorhynchus mykiss	-	PHY	5.2	FW	-	-	R	-	Carballo, 1992	4
Oncorhynchus mykiss	NOEC	PHY	≤ 9.6	FW	12	d	F	12.5	Ruby *et al*, 1986	2
Oncorhynchus mykiss	NOEC	PHY	< 10	FW	28	d	F	10	Leduc and Chan, 1975	2
Oncorhynchus tshawytscha	-	PHY	10	FW	2	month	F	-	Negilski, 1973	4

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration[a] ($\mu g\ CN^-/l$)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Oncorhynchus mykiss	-	PHY	19.3	FW	-	-	F	-	Speyer, 1975	4
Salmo salar	-	PHY	20	FW	170	d	F	-	Leduc, 1978	3
Salmo trutta	-	PHY	25	FW	300	min	S	-	Carter, 1962	4
Salmo salar	-	PHY	40	FW	170	d	F	-	Leduc, 1978	3
Oncorhynchus mykiss	-	PHY	52	FW	24	h	F	20	Slooff, 1979	2
Oncorhynchus mykiss	-	PHY	130	FW	≤ 24	h	F	-	Slooff, 1978	4
Oncorhynchus tshawytscha	-	POP	10	FW	2	month	F	-	Negilski, 1973	4
Oncorhynchus tshawytscha	-	POP	10	FW	5	month	F	-	Negilski, 1973	4
Oncorhynchus mykiss	NOEC	REP	0.04	FW	0.67	d	S	10	Billard and Roubaud, 1985	3
Salvelinus fontinalis	NOEC	REP	5.4	FW	144	d	F	-	Koenst *et al*, 1977	2
Oncorhynchus mykiss	NOEC	REP	40	FW	0.67	h	S	10	Billard and Roubaud, 1985	3
Salvelinus fontinalis	NOEC	REP	52	FW	144	d	F	-	Koenst *et al*, 1977	2
Oncorhynchus mykiss	-	REP	> 400	FW	0.67	h	S	-	Billard and Roubaud, 1985	3

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration[a] (µg CN^-/l)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Lagodon rhomboides	LC_{50}	MOR	66.5	SW	24	h	S	13.7 - 20.4	Daugherty and Garrett, 1951	3
Insecta										
Coleoptera										
Dytiscus	LC_{50}	MOR	246	FW	96	h	S	21.5	Sarkar, 1990	2
Dytiscus	LC_{50}	MOR	220	FW	96	h	S	26.5	Sarkar, 1990	2
Dytiscus	LC_{50}	MOR	259	FW	96	h	S	31.4	Sarkar, 1990	2
Diptera										
Aedes aegypti	ET_{50}*	ITX	530	FW	> 5	h	S	-	Burchfield and Storrs, 1954	3
Aedes aegypti	ET_{50}*	ITX	5,300	FW	0.72	h	S	-	Burchfield and Storrs, 1954	3
Tanytarsus dissimilis	EC_{50}	MOR	648	FW	24	h	-	-	Call *et al*, 1979	4
Tanytarsus dissimilis	LC_{50}	MOR	1,285	FW	48	h	-	-	Call *et al*, 1979	4
Tanytarsus dissimilis	LC_{50}	MOR	2,490	FW	48	h	S	-	Call *et al*, 1983	4
Tanytarsus dissimilis	LC_{50}	MOR	8,990	FW	24	h	S	-	Call *et al*, 1983	4
Ephemeroptera										
Stenonema rubrum	LC_{50}	MOR	500	FW	48	h	-	-	Roback, 1965	4

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration[a] ($\mu g\ CN^-/l$)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Heteroptera										
Ranatra sp.	LC_{50}	MOR	228	FW	96	h	S	31.4	Sarkar, 1990	2
Ranatra sp.	LC_{50}	MOR	229	FW	96	h	S	21.5	Sarkar, 1990	2
Ranatra sp.	LC_{50}	MOR	232	FW	96	h	S	26.5	Sarkar, 1990	2
Nepa sp.	LC_{50}	MOR	242	FW	96	h	S	31.5	Sarkar, 1990	2
Corixa sp.	LC_{50}	MOR	247	FW	96	h	S	21.5	Sarkar, 1990	2
Corixa sp.	LC_{50}	MOR	251	FW	96	h	S	26.5	Sarkar, 1990	2
Corixa sp.	LC_{50}	MOR	252	FW	96	h	S	31.4	Sarkar, 1990	2
Nepa sp.	LC_{50}	MOR	289	FW	96	h	S	21.5	Sarkar, 1990	2
Nepa sp.	LC_{50}	MOR	294	FW	96	h	S	26.5	Sarkar, 1990	2
Plecoptera										
Pteronarcys dorsata	EC_{50}	BEH	426	FW	96	h	F	-	Call and Brooke, 1982	4
Pteronarcys dorsata	LC_{50}	MOR	436	FW	96	h	F	-	Call and Brooke, 1982	4
Trichoptera										
Hydropsyche sp.	LC_{50}	MOR	2,000	FW	48	h	-	-	Roback, 1965	4

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration[a] (µg CN^-/l)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Invertebrates (miscellaneous)										
Invertebrates	-	POP	10	FW	5	month	F	-	Negilski, 1973	4
Invertebrates	-	POP	10	FW	2	month	F	-	Negilski, 1973	4
Invertebrates	-	POP	10	FW	2	month	F	-	Negilski, 1973	4
Invertebrates	-	POP	10	FW	5	month	F	-	Negilski, 1973	4
Macrophytes										
Myriophyllum spicatum	EC_{50}	GRO	27,300	FW	32	d	S	20	Stanley, 1974	2
Myriophyllum spicatum	EC_{50}	GRO	28,600	FW	32	d	S	20	Stanley, 1974	2
Myriophyllum spicatum	EC_{50}	POP	20,000	FW	32	d	S	20	Stanley, 1974	2
Myriophyllum spicatum	EC_{50}	POP	22,400	FW	32	d	S	20	Stanley, 1974	2
Mollusca										
Physa heterostropha	LC_{20}	MOR	43.2	FW	96	h	S	20	Academy of Natural Sciences, 1960	2
Physa heterostropha	LC_{50}	MOR	190	FW	96	h	S	20	Academy of Natural Sciences, 1960	3
Physa heterostropha	LC_{50}	MOR	272	FW	96	h	S	30	Academy of Natural Sciences, 1960	2
Physa heterostropha	LC50	MOR	280	FW	96	h	S	30	Academy of Natural Sciences, 1960	2
Physella heterostropha	LC50*	MOR	432	FW	96	h	S	18	Cairns and Scheier, 1958	2

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration[a] ($\mu g\ CN^-/l$)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Physella heterostropha	LC_{50}	MOR	432	FW	96	h	S	18	Cairns and Scheier, 1958	2
Physa heterostropha	LC_{50}	MOR	740	FW	96	h	S	20	Academy of Natural Sciences, 1960	2
Pila globosa	LC_{50}	MOR	892	FW	96	h	S	31.4	Sarkar, 1990	2
Lymnaea luteola	LC_{50}	MOR	1,316	FW	96	h	S	21.5	Sarkar, 1990	2
Lymnaea luteola	LC_{50}	MOR	1,317	FW	96	h	S	31.5	Sarkar, 1990	2
Lymnaea luteola	LC_{50}	MOR	1,344	FW	96	h	S	26.5	Sarkar, 1990	2
Physa sp.	NR-LETH	MOR	1,381	FW	-	-	-	-	Lewis and Tarrant, 1960	3
Viviparus bengalensis	LC_{50}	MOR	1,532	FW	96	h	S	31.4	Sarkar, 1990	2
Pila globosa	LC_{50}	MOR	1,540	FW	96	h	S	26.5	Sarkar, 1990	2
Viviparus bengalensis	LC_{50}	MOR	1,540	FW	96	h	S	21.5	Sarkar, 1990	2
Pila globosa	LC_{50}	MOR	1,572	FW	96	h	S	21.5	Sarkar, 1990	2
Viviparus bengalensis	LC_{50}	MOR	1,577	FW	96	h	S	26.5	Sarkar, 1990	2
Physa integra	LC_{50}	MOR	2,400	FW	24	h	R	-	Cairns *et al*, 1976	4
Lymnaea emarginata angulata	LC_{50}	MOR	3,300	FW	24	h	R	-	Cairns *et al*, 1976	4
Lymnaea emarginata angulata	LC_{50}	MOR	3,300	FW	48	h	R	-	Cairns *et al*, 1976	4
Anculosa sp.	LC_{50}	MOR	7,000	FW	48	h	S	25	Cairns *et al*, 1978	2

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration[a] ($\mu g\ CN^-/l$)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Anculosa sp.	LC_{50}	MOR	7,600	FW	24	h	S	25	Cairns *et al*, 1978	2
Anculosa sp.	LC_{50}	MOR	8,000	FW	48	h	S	20	Cairns *et al*, 1978	2
Bithynia tentaculata	LC_{50}	MOR	9,900	FW	48	h	-	11.5	Gillar, 1962	4
Anculosa sp.	LC_{50}	MOR	10,000	FW	48	h	S	15	Cairns *et al*, 1978	2
Anculosa sp.	LC_{50}	MOR	10,000	FW	24	h	S	20	Cairns *et al*, 1978	2
Anculosa sp.	LC_{50}	MOR	11,000	FW	24	h	S	15	Cairns *et al*, 1978	2
Anculosa sp.	LC_{50}	MOR	12,800	FW	48	h	S	10	Cairns *et al*, 1978	2
Anculosa sp.	LC_{50}	MOR	13,000	FW	24	h	S	10	Cairns *et al*, 1978	2
Anculosa sp.	LC_{50}	MOR	13,600	FW	48	h	S	5	Cairns *et al*, 1978	2
Anculosa sp.	LC_{50}	MOR	14,000	FW	24	h	S	5	Cairns *et al*, 1978	2
Mytilus edulis	LC_{50}	MOR	36,000	SW	96	h	S	-	Abel, 1976	2
Helisoma trivolvis	LC_{50}	MOR	> 50,000	FW	96	h	S	20	Ewell *et al*, 1986	3
Lymnaea sp.	EC_{50}*	MOR	52,000	FW	96	h	S	-	Dowden and Bennett, 1965	4
Lymnaea sp.	EC_{50}*	MOR	58,800	FW	72	h	S	-	Dowden and Bennett, 1965	4
Physa integra	LC_{50}	MOR	135,000	FW	48	h	R	-	Cairns *et al*, 1976	4
Lymnaea sp.	EC_{50}*	MOR	318,000	FW	48	h	S	-	Dowden and Bennett, 1965	4
Lymnaea sp.	EC_{50}*	MOR	318,000	FW	24	h	S	-	Dowden and Bennett, 1965	4

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration[a] ($\mu g\ CN^-/l$)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Elimia livescens	LC_{50}	MOR	760,000	FW	48	h	R	-	Cairns *et al*, 1976	4
Elimia livescens	LC_{50}	MOR	940,000	FW	24	h	R	-	Cairns *et al*, 1976	4
Mytilus edulis	NOEC	PHY	< 18	SW	14	d	F	15	Thompson, 1984	2
Mytilus edulis	LC_{20}	PHY	100	SW	14	d	F	15	Thompson, 1984	2
Ostrea gigas	-	PHY	130	SW	3	h	-	25	Usuki, 1956	3
Bivalvia										
Chlamys asperrimus	NOEC	DVP	5	SW	48	h	S	18	Pablo *et al*, 1997b	2
Chlamys asperrimus	LOEC	DVP	10	SW	48	h	S	18	Pablo *et al*, 1997b	2
Mytilus galloprovincialis	EC_{50}	DVP	10.6	SW	48	h	S	-	Pavicic and Pihlar, 1982	2
Chlamys asperrimus	EC_{50}	DVP	28.6	SW	48	h	S	18	Pablo *et al*, 1997b	2
Mytilus galloprovincialis	NOEC	GRO	3.2	SW	48	h	S	20	Pavicic and Pihlar, 1982	2
Mytilus galloprovincialis (veliger)	LC_{50}	MOR	154	SW	48	h	S	-	Pavicic and Pihlar, 1982	2
Anodonta sp.	-	MOR	1,593	FW	-	-	-	-	Lewis and Tarrant, 1960	3
Crepidula fornicata	LC_{50}	MOR	> 10,000	SW	96	h	-		Gardner, 1981	4
Crepidula fornicata	LC_{50}	MOR	> 10,000	SW	-	-	-	-	Brix *et al*, 2000	2
Cerastoderma edule	LC_{50}	MOR	> 25,000	SW	48	h	R		Portmann and Wilson, 1971	3
Scapharca inaequivalvis	LT_{50}	MOR	26,000	SW	9.8	d	S	18	De Zwaan *et al*, 1993	3

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration[a] ($\mu g\ CN^-/l$)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Oligochaeta										
Aeolosoma headleyi	LC_{50}	MOR	9,000	FW	48	h	S	10	Cairns *et al*, 1978	2
Aeolosoma headleyi	LC_{50}	MOR	10,000	FW	48	h	S	5	Cairns *et al*, 1978	2
Aeolosoma headleyi	LC_{50}	MOR	11,000	FW	24	h	S	5	Cairns *et al*, 1978	2
Lumbriculus variegatus	LC_{50}	MOR	11,000	FW	96	h	S	20	Ewell *et al*, 1986	2
Limnodrilus sp.	LC_{50}	MOR	25,000	FW	48	h	C	18.5	Gillar, 1962	4
Aeolosoma headleyi	LC_{50}	MOR	100,000	FW	24	h	S	10	Cairns *et al*, 1978	2
Aeolosoma headleyi	LC_{50}	MOR	120,000	FW	48	h	S	15	Cairns *et al*, 1978	2
Aeolosoma headleyi	LC_{50}	MOR	120,000	FW	24	h	S	15	Cairns *et al*, 1978	2
Aeolosoma headleyi	LC_{50}	MOR	160,000	FW	24	h	S	20	Cairns *et al*, 1978	2
Aeolosoma headleyi	LC_{50}	MOR	160,000	FW	24	h	S	20	Cairns *et al*, 1978	3
Aeolosoma headleyi	LC_{50}	MOR	160,000	FW	48	h	S	20	Cairns *et al*, 1978	2
Aeolosoma headleyi	LC_{50}	MOR	160,000	FW	48	h	S	25	Cairns *et al*, 1978	2
Protozoa										
Spirostomum ambiguum	EC_{50}	DVP	1,180	FW	48	h	S	25	Nalęcz-Jawecki and Sawicki, 1998	2
Spirostomum ambiguum	EC_{50}	DVP	1,280	FW	24	h	S	25	Nalęcz-Jawecki and Sawicki, 1998	2
Spirostomum ambiguum	LC_{50}	MOR	2,040	FW	48	h	S	25	Nalęcz-Jawecki and Sawicki, 1998	2
Spirostomum ambiguum	LC_{50}	MOR	2,140	FW	24	h	S	25	Nalęcz-Jawecki and Sawicki, 1998	2

Table J: Aquatic toxicity records (cont'd)

Species	Endpoint	Effect	Concentration [a] (µg CN^-/l)	Medium	Duration	Unit	Exposure type	T (°C)	Reference	CoR
Tetrahymena pyriformis	-	PHY	50	FW	0.08	h	S	-	Slabbert and Maree, 1986	4
Uronema parduczi	-	POP	108	FW	-	-	-	-	Bringmann and Kühn, 1981	4
Uronema parduczi	-	POP	143	FW	20	h	-	-	Bringmann and Kühn, 1980a	3
Flagellata										
Entosiphon sulcatum	-	POP	720	FW	-	-	-	-	Bringmann and Kühn, 1979	3
Entosiphon sulcatum	-	POP	720	FW	-	-	-	-	Bringmann and Kühn, 1981	4
Entosiphon sulcatum	-	POP	956	FW	72	h	S	-	Bringmann and Kühn, 1978a	4
Rotatoria										
Philodina acuticornis	LC_{50}	MOR	54,000	FW	48	h	S	20	Cairns *et al*, 1978	2
Brachionus calyciflorus	LC_{50}	MOR	62,500	FW	24	h	-	-	Calleja *et al*, 1994	4
Turbellaria										
Dugesia tigrina	LC_{50}	MOR	2,100	FW	96	h	S	20	Ewell *et al*, 1986	2
Dugesia tigrina	LC_{50}	MOR	19,400	FW	96	h	S	20	See *et al*, 1974	4

[a] Several values have been converted

[b] Almost all references with CoR 4 cited by US-EPA, 2003

[c] Reported as *Squalius cephalus*

APPENDIX K: ABSORBED DOSE OF CYANIDE IN THE 28-DAY AND 90-DAY INHALATION STUDIES ON ACETONE CYANOHYDRIN IN RATS

To elucidate the difference in the internal dose levels in animals exposed to approximately the same concentrations of ACH in the 28-day and 90-day inhalation studies in rats (Monsanto, 1981d, 1984), the Task Force calculated the lethal doses in the 28-day study for the animals that died following day one and for animals exposed to the highest single concentration in the 90-day study (on day 52).

The following assumptions were made:

1. Inhalation volume for rats in a 28-day study: 175 ml/min (ECB, 2003);
2. Inhalation volume for rats in a 90-day study: 200 ml/min (ECB, 2003);
3. Initial body weights for the 3 male rats that died in the 28-day study on day 1 (body weights at the time of death): 257, 258 and 258 g;
4. Body weights of rats in the 90-day study on day 52 that were exposed on day 56 to similar peak concentrations as the rats that died in the 28-day study (body weight closest to the date of highest exposure): 431 g (male mean) and 363 g (lowest individual);
5. 50% absorption after inhalation exposure.

In the 28-day study, 3 male animals died on day 1 after a peak exposure of 63.5 ppm ACH (224 mg/m^3, 0.224 mg/l). The exposure duration was 6 hours. With an inhalation volume of 175 ml/min the rats would have inhaled 63 l of the test atmosphere and 14.1 mg ACH. Assuming 50% absorption, the amount absorbed is 7 mg ACH per animal. For the animals of 257 or 258 gbw this corresponds to a dose of 27.2 or 27.1 mg ACH/kgbw (8.1 mg CN^-/kgbw).

In the 90-day study, the highest peak exposure occurred on day 56 at 66 ppm ACH (233 mg/m3, 0.233 mg/l). The exposure duration was 6 hours. With an inhalation volume of 200 ml/min the rats would have inhaled 72 l of the test atmosphere and 16.8 mg of ACH. Assuming 50% absorption, the amount absorbed is 8.4 mg ACH per animal. The mean body weight of male rats at this time of the study was approximately 431 g (determined on day 52) and the corresponding inhaled dose is 19.5 mg ACH/kgbw (5.85 mg CN^-/kgbw). For the smaller animal of 363 gbw the dose would correspond to 23 mg ACH/kgbw (6.9 mg CN^-/kgbw).

Given the steep dose response curve of cyanide, this difference in systemic dose can explain the acute lethality in the 28-day study and the absence of lethality at approximately the same exposure concentrations in the 90-day study.

APPENDIX L: EVALUATION OF SCHULZ *ET AL*, 1982 AND SCHULZ, 1984

L.1 General observations

Schulz *et al* (1982) reported on cyanide blood levels in 51 people infused with sodium nitroprusside dihydrate at different infusion rates (Section 7.3). Sodium nitroprusside releases 44% of its weight as CN^-, which immediately forms HCN in the body.

At a certain infusion rate of sodium nitroprusside, blood levels of cyanide were increasing. This phenomenon was considered by Schulz *et al* (1982) to indicate the infusion rate at which the detoxifying capacity of the body is overwhelmed and above which death will finally occur. However, apart from rhodanese, other enzyme systems may become involved with increasing infusion rate and a new higher steady-state level of cyanide may occur in the blood. That level is still below a toxic concentration level. So an increased cyanide level in the blood of more than 20 nmol/ml in erythrocytes does not indicate a fatal case of long-term poisoning. According to the authors, clinical symptoms of intoxication were observed at levels above 200 nmol/ml erythrocytes and fatalities at 400 nmol/ml. This will be illustrated with human and animal studies.

In the paper of Schulz *et al* (1982), Figure 1 presents cyanide levels during and after sodium nitroprusside infusion of 51 patients. However, toxic levels leading to clinical symptoms were not achieved (150 nmol/m1 erythrocytes without effects according to Schulz *et al,* 1982; Schulz, 1984) and there was no observation time after 180 minutes. Unfortunately, individual infusion rates and duration of infusion were not included in the information, from which Figure 1 was derived. Therefore no conclusions can be drawn as to individual blood levels over time. Figure 1 cannot be used for a toxicokinetic analysis.

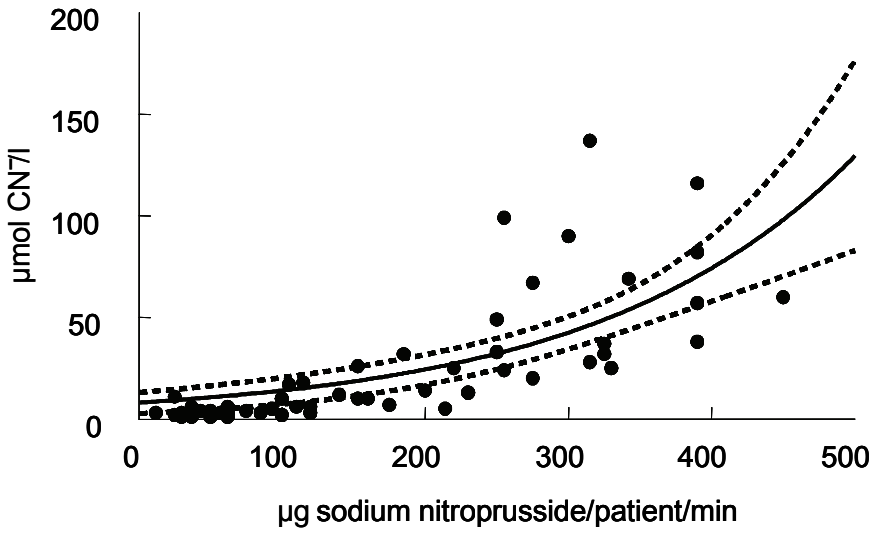
It has been observed in animal studies in rats that at higher dose levels, a smaller percentage of CN is detoxified via rhodanese; other pathways are also active. Hébert (1993) reported on rats exposed via drinking water to NaCN (Section 7.3). It can be estimated from the data, that at a dose level of 55 µmol CN/kgbw/d about 76% is detoxified via the rhodanese pathway but at a level of 480 µmol CN/kgbw/d this is only 53%.

Similar evaluation of the study of Leuschner *et al* (1991) (Section 7.3) reveals that at dose levels from 600 µmol CN/kgbw/d and higher, no more than 15% was detoxified via the rhodanese pathway. Moreover, Leuschner *et al* (1991) showed that an increase of the dose rate of cyanide by enhanced levels of cyanide in the drinking water resulted in a dose-dependent increase of cyanide blood levels without mortality over a period of 13 weeks. However, Leuschner *et al* (1991) reported levels in total blood, while Schulz *et al* (1982) and Schulz (1984) reported levels in erythrocytes.

L.2 Quantitative analysis of the data in 51 patients (Schulz et al, 1982)

Figure 2 (maximum cyanide levels in patients as a function of mean sodium nitroprusside dosage rate) of the paper of Schulz *et al* (1982) was used for the quantitative analysis. Individual data points (infusion rates and corresponding cyanide level in erythrocytes) were obtained by magnifying the figure to A4-size and reading off the coordinates with a ruler. In Figure 2, 52 data points were identified, while the authors stated 51 cases. The 52 data points were subjected to non-linear regression analysis and a mathematical equation derived for the relationship between infusion rate of sodium nitroprusside and the cyanide level in erythrocytes for an average infusion period of 80 minutes (Figure L).

Figure L: Cyanide level in erythrocytes at increasing sodium nitroprusside infusion rate[a]



[a] • data point, —— regression equation, with 95% confidence interval (- - - -)

Where

CN^--level erythrocytes = $b_0 \times \exp(b_1 \times \text{dose})$

Residual squares = 514.9

Degrees of Freedom = 50

Fraction variance explained = 0.51, i.e. 51%

$b_0 = 7.97$ Student t for $b_0 = 3.03$

$b_1 = 0.0056$ Student t for $b_1 = 5.86$

Variance b_0 b_0 = 6.92

Covariance b_0 b_1 = –0.0024

Variance b_1 b_1 = 0.91×10^{-6}

This relationship can be used to derive sodium nitroprusside infusion rates (with 95% confidence) that will not exceed a fixed level of cyanide in erythrocytes (Table L).

Table L: Infusion rate of sodium nitroprusside derived from cyanide level in erythrocytes

Maximum cyanide concentration (µmol CN^-/l) (95% confidence)	**Infusion rate of sodium nitroprusside (µg/min/patient)**
20	107
30	196
40	258
50	303
100	420
150	482
200	526
250	559
300	587

Schulz (1984) stated that cyanide levels in erythrocytes of less than 150 µmol/l usually caused no recognisable symptoms. From Table L.1 it can be seen that this is equivalent to an infusion for 80 minutes at a rate of 482 µg sodium nitroprusside/min (i.e. erythrocyte CN level of 150 µmol/l will not be exceeded with 95% confidence). The sodium nitroprusside infusion rate can be converted to an equivalent cyanide infusion rate by multiplying by 0.44 (44% of sodium nitroprusside is CN^-) to give an infusion rate of 212 µg CN^-/min per patient or 3.0 µg µg CN/kgbw/min (assuming a body weight of 70 kg). This infusion rate, if given over an 80-minute period, will not cause overt symptoms of cyanide poisoning with 95% confidence.

Also according to Schulz (1984), fatal poisoning started to occur at a cyanide erythrocyte level of 300 µmol/l. From Table L.1 it can be seen that this is equivalent with an infusion rate of 587 µg sodium nitroprusside/min (i.e. a level of 300 µmol CN^-/l in erythrocytes will not be exceeded at 95% confidence), equivalent to (multiplied by 0.44) 258 µg CN^-/min per patient or of 3.7 µg CN^-/kgbw/min (assumed bodyweight of 70 kg). At this cyanide infusion rate, the cyanide level of 300 µmol CN^-/l in erythrocytes will not be exceeded with 95% confidence. The 3.7 µg CN^-/kgbw/min threshold to mortality might also be regarded as the lower estimate (5th percentile) of the human detoxifying rate of cyanide. The corresponding point estimate of the human detoxifying rate is 4.1 µg CN^-/kgbw/min.

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