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PIPERAZINE

CAS No: 110-85-0

EINECS No: 203-808-3

Summary Risk Assessment Report

2005 **Special Publication I.05.72**

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SUMMARY RISK ASSESSMENT REPORT

Final report, 2005

Sweden

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PREFACE

This report provides a summary, with conclusions, of the risk assessment report of the substance piperazine that has been prepared by Sweden in the context of Council Regulation (EEC) No. 793/93 on the evaluation and control of existing substances.

For detailed information on the risk assessment principles and procedures followed, the underlying data and the literature references the reader is referred to the comprehensive Final Risk Assessment Report (Final RAR) that can be obtained from the European Chemicals Bureau[1]. The Final RAR should be used for citation purposes rather than this present Summary Report.

[1] European Chemicals Bureau – Existing Chemicals – http://ecb.jrc.it

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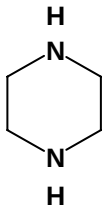
TABLES

1 GENERAL SUBSTANCE INFORMATION

1.1 IDENTIFICATION OF THE SUBSTANCE

CAS Number:	110-85-0 Piperazine is also available as hexahydrate, CAS No. 142-63-2.
EINECS Number:	203-808-3
IUPAC Name:	Piperazine
Synonyms:	1,4-Piperazine 1,4-Diazacyclohexane Diethylenediamine Hexahydropyrazine Piperazidine
Conversion factors	1 ppm = 3.58 mg/m^3; 1 mg/m^3 = 0.279 ppm
Molecular weight:	86.14
Molecular formula:	$C_4H_{10}N_2$
Structural formula:	



1.2 PURITY/IMPURITIES, ADDITIVES

The declared purity of a commercial available piperazine product (as free base) is ≥ 99.9% w/w.

The only declared impurity is water. Trace amounts of mononitropiperazine in the range 0.06-0.08 ppb have however been reported in commercial piperazine. No additives are reported.

1.3 PHYSICO-CHEMICAL PROPERTIES

The physico-chemical properties are summarised in **Table 1.1**.

Table 1.1 Summary of physico-chemical properties

Property	Value/Remark
Physical state	At room temperature, anhydrous piperazine forms white or translucent, rhomboid, or flake like crystals that are highly hygroscopic. Piperazine base is available either as colourless, hygroscopic, crystalline chips or as a solution in water. The concentration is usually 64-69%. The water solution is, as a rule, a white mass. Piperazine is highly basic (pH>12), with two dissociation constants, pKa_1 is 9.7 and pKa_2 is 5.3. Piperazine hexahydrate is soluble in water; with a pH assumingly slightly lower than that of the base (the content of piperazine is the hexahydrate is 44%). The piperazine salts are slightly acidic
Melting point	107°C
Boiling point	147.7°C
Density	1.1 g/cm^3 at 20°C
Vapour pressure	0.44 mbar (44 Pa) at 24.2°C
Solubility	150 g/l at 20°C and pH 12 Piperazine salts differ in solubility from very slightly soluble to freely soluble in water
Partition coefficient n-octanol/water	-1.24 at 25°C
Flash point	65°C
Autoflammability	Not applicable
Explosivity	Explosion limits in air: 4-14 % (volume)
Oxidising properties	None
Other physico-chemical properties	Reactions of the piperazine base with acids are exothermic. Piperazine absorbs CO_2 from the atmosphere. In acid solution, piperazine is converted to N-mononitrosopiperazine in the presence of nitrite.

1.4 CLASSIFICATION

Current classification (22nd ATP):

Classification: C; R 34 R42/43 R52/53
Labelling: C; R34-42/43-52/53
S(1/2)-22-26-36/37/39-45-61

The Meeting of the Technical Committee C&L on the Classificatin and Labelling of Dangerous Substances in September 2004 recommended the following classification and labelling of piperazine to be entered in Annex I of Directive 67/548/EEC, 30th ATP (index-no 612-057-00-4 (solid) and 612-057-01-1 (liquid)):

Piperazine [solid]

Classification: Repro. Cat. 3; R62-63 C; R 34 R42/43
Labelling: Xn; C; R34-42/43-62-63
S(1/2)-22-26-36/37/39-45

Piperazine [liquid]

Classification: Repro. Cat. 3; R62-63 C; R 34 R42/43
Labelling: Xn; C; R34-42/43-62-63

S(1/2)-23-26-36/37/39-45

2 GENERAL INFORMATION ON EXPOSURE

2.1 PRODUCTION

In 1996/1997 piperazine was produced by 4 plants situated in 4 different EU member states, one company ceased with the production of piperazine free base in 1999. The United States and Japan are known to produce piperazine and export to the EU.

At present, there are two production methods used, the ethanolamine based process and the ethylene chloride based process.

2.2 USES

Piperazine, as such or as salts, is mainly used as an intermediate in chemical industry including production of pharmaceuticals. Piperazine, as such or as salts, is used also for human and veterinary medicinal drugs, as formulation in gas-washing (scrubbers), and as a catalyst in urethane production.

Piperazine is used as a functional ingredient in gas-washer liquids. Within EU there are 33 plants that are using this gas-washing system. Gas washing, gas cleaning, or gas absorption, is a unit operation in the chemical industry to separate components of a gas mixture by washing or scrubbing with a liquid. One or more of the constituents of the gas mixture dissolves or is absorbed in the liquid and can thus be removed from the mixture. The gas-washing liquid is (often) recovered in a subsequent stripping or desorption operation. This second step is often the reverse of the absorption step. Release of constituents of the solvent may take place at the regeneration, mainly as gas or vapour. The liquid solvent phase is recycled after the desorption operation and a release of liquid is not likely to occur during the process. However, at intervals of 3-5 years the gas washer plants are cleaned, and process water with significant amounts of piperazine is released to waste water.

3 ENVIRONMENT

3.1 ENVIRONMENTAL EXPOSURE

Predicted environmental concentrations are shown together with risk characterisation ratios in **Table 3.2**, **Table 3.3** and **Table 3.4**

3.1.1 Environmental releases

Releases to the environment at the local scale have been considered for the following:

- Production of piperazine
- Processing of piperazine to salts and processing of piperazine as intermediates
- Formulation of piperazine as such or as its salts
- Use of gas washing formulations
- Private use of pharmaceuticals with piperazine, its salts and derivatives
- Use of manure from animals treated with piperazine (anthelmintics) as fertiliser on agricultural fields and grassland.

Exposure to man via the environment has been considered for the following:

- Intake of contaminated drinking water and fish originating from surface water associated to local industrial sites or municipal STP.
- Intake of contaminated groundwater associated to agricultural fields fertilised with manure from animals treated with piperazine in anthelmintics.
- Intake of contaminated crops from agricultural fields fertilised with manure from animals treated with piperazine in anthelmintics.
- Inhalation of piperazine after emissions to air from the use of gas washer formulations.
- Intake of contaminated foodstuff after emissions to air and surface water from the use of gas washer formulations.

Releases from production and processing sites

Site-specific information on the annual release of piperazine to the aquatic environment is available for six point sources out of eight. For two production sites, emissions to surface water are claimed to be zero, since the “effluent” is incinerated. Information on annual release to air is available for three production sites and four processing sites.

No direct release of piperazine to soil is reported from local point sources, and no significant aerial deposition or exposure via sludge is expected.

3.1.2 Environmental fate

Piperazine can be assumed to be rapidly photolysed in the atmosphere; the half-life was calculated to be 0.8 hours. In natural water it is considered to be stable towards photolysis. From non-standard studies it can be expected that piperazine is hydrolytically stable under environmentally relevant conditions.

Piperazine is not readily biodegradable but can be considered to be inherently degradable.

There is no considerable potential for bioaccumulation; a BCF of < 3.9 for *Cyprinus carpio* is reported.

3.2 EFFECTS ASSESSMENT

The predicted no effect concentrations in different environmental compartments are summarised in **Table 3.1**.

Table 3.1 Predicted no effect concentrations (PNEC) of piperazine in different environmental compartments.

Compartment	Endpoint to be used in the calculation	Assessment factor with justification	PNEC
Aquatic compartment	21-day NOEC 12.5 mg/L for *Daphnia*	10, since a long term study was available for the most sensitive species.	1.25 mg/L
Sediment	No data. Estimated from PNECaqua by equilibrium partitioning method.	10, since a long term study was available for the most sensitive species.	(0.75 mg/kg ww)
Micro-organisms in STP	0.5-hour NOEC 540 mg/L in respiration inhibition test	10, as given in TGD	54 mg/L
Atmospheric compartment	No data	-	-
Terrestrial compartment	Estimated from PNECaqua by equilibrium partitioning method.	10, since a long term study was available for the most sensitive species.	6.0 mg/kg ww

3.2.1 Aquatic compartment (incl. sediment)

From the available data on the effects to aquatic organisms, *Daphnia* appears to be the most sensitive species with a 48-hour EC_{50} of 21 mg/L and a 21-day NOEC for reproduction of 12.5 mg/L. The available studies on fish and algae indicate that piperazine is not acutely toxic to the tested species at concentrations up to 1 g/L.

Effects on microorganisms

The $PNEC_{micro\text{-}organisms}$ based on the available respiration inhibition test is 540/10 = 54 mg/L.

Effects assessment for the sediment

No data are available for sediment-dwelling organisms, and therefore the $PNEC_{sediment}$ is estimated from $PNEC_{surface\ water}$ using the equilibrium partitioning equation. Since both exposure and effects levels in sediment are extrapolated with the equilibrium partitioning method, the risk for sediment organisms is covered by the surface water assessment.

3.2.2 Atmosphere

There are no effect data for the atmospheric environment available.

3.2.3 Terrestrial compartment

Since no standard test data on terrestrial organisms are available, the $PNEC_{soil}$ is estimated from $PNEC_{water}$. The calculated $PNEC_{soil}$ = 6.0 mg/kg ww.

Even though a possible route of exposure for soil is via the use of piperazine as an anthelmintic for domestic animals, it is considered enough to derive the PNEC from a sensitive aquatic species, i.e. *Daphnia magna* in a long term toxicity test. An experimental PNEC needs to be 50,000 times lower than the calculated one to reach a PEC/PNEC above 1. In case the use of piperazine for veterinary medical purposes increases this conclusion needs to be reconsidered. A scenario has been constructed where manure from indoor stocks of piglets and chickens is spread on arable land. The predicted local concentrations in soil after use of piperazine as anthelmintic were calculated according to a model for veterinary products.

3.2.4 Secondary poisoning

No significant bioaccumulation or biomagnification is expected.

3.3 RISK CHARACTERISATION

3.3.1 Aquatic compartment (incl. sediment)

Calculated local predicted environmental concentrations and PEC/PNEC ratios for surface water and sediment at known industrial point sources of piperazine are listed in **Table 3.2**.

Table 3.2 Calculated local predicted environmental concentrations and PEC/PNEC ratios for surface water and sediment at known industrial point sources of piperazine.

Site	Life cycle stage	PEClocal, during emission (mg/L)	PEClocal (mg/kg ww)	PEC/PNEC Aquatic
		Surface water	Sediment	
A	Production	0.002*	0.002*	0.0014
B	Production	0.001*	0.001*	0.0005
C	Production	1.5	1.2	1.2**
D	Production / processing / formulation	0.20*	0.16*	0.16
E	Processing	0.001*	0.001*	0.0005
F	Processing / formulation	0.001*	0.001*	0.0008
G	Processing / formulation	0.002*	0.002*	0.0014
H	Formulation	4.9	3.8	3.9**

* Figures based on site specific information.
** Bold figures for PEC/PNEC ratio indicate concern.

Calculated local predicted environmental concentrations and PEC/PNEC ratios for surface water and sediment for a generic local gas washer site and private use of pharmaceuticals are listed in **Table 3.3**.

Table 3.3 Calculated local predicted environmental concentrations (PEClocal) and PEC/PNEC ratios of piperazine in surface water and sediment for a generic local gas washer site and private use of pharmaceuticals. Concentrations during emission episodes for surface water, annual mean for sediment.

Life cycle stage	PEClocal, during emission surface water (mg/L)	PEClocal, annual mean sediment (mg/kg ww)	PEC/PNEC aquatic
Industrial use of gas washers	0.02 – 29	0.01 – 23	0.02 – 23*
Private use of pharmaceuticals	0.002	0.002	0.0002

* Bold figures for PEC/PNEC ratio indicate concern

There is a need for limiting the risks (risk reduction measures, which are already being applied, shall be taken into account). This applies to aquatic organisms in the local Production scenario C, local Formulation scenario H and for 21 out of 33 local scenarios for down-stream users of gas-washer formulations. It also applies for micro-organisms in the STP for the majority of the local gas washer scenarios.

3.3.2 Atmosphere

No data are available on effects in the atmospheric compartment.

The calculated concentrations in air were low at all local point sources. However, higher local concentrations may occur at the industrial use of gas washer formulations. The highest estimated annual mean concentration was approximately 0.4 μg/m^3.

3.3.3 Terrestrial compartment

Regional and continental predicted environmental concentrations and PEC/PNEC ratios for the terrestrial environment are given in **Table 3.4**.

Table 3.4 Regional and continental predicted environmental concentrations and PEC/PNEC ratios in agricultural soil calculated based on generic scenarios. Local predicted concentration in soil (grassland) after fertilising with manure from animals treated with piperazine

	PEC $_{agric\ soil}$ (μg/kg ww)	PEC/PNEC$_{soil}$
Regional	0.0002	0.000000003
Continental	0.000006	0.000000001
Local	120	0.02

There is at present no need for further information and/or testing and no need for risk reduction measures beyond those, which are being applied already.

3.3.4 Secondary poisoning

BCF is determined to be <4 and the risk for accumulation in biota is assessed to be insignificant. Hence, the risk for biomagnification and/or secondary poisoning is considered to be negligible.

4 HUMAN HEALTH

4.1 HUMAN HEALTH (TOXICITY)

4.1.1 Exposure assessment

Due to the use of piperazine in the society, humans may be exposed from different sources: 1) at the workplace at the sites manufacturing piperazine, at the industrial uses of piperazine and piperazine salts and at the industrial end-uses of products containing piperazine and piperazine derivatives; 2) from use of consumer products; and, 3) indirectly via the environment via food, soil, water and air.

Piperazine is used in veterinary pharmaceuticals as anthelmintics, i.e., drugs that act against infections caused by parasitic worms. Formerly, piperazine was also used in human medicine. Piperazine is also used as hardener for pre-polymers for glue, in gas washer formulations, as intermediate for urethane catalysts, and as an intermediate for a number of pharmaceuticals. An overview of the uses of piperazine is given in **Table 4.1**.

Table 4.1 Use pattern of piperazine and examples of end products and their use

Material	Function of piperazine	Product	Function of product	End products (examples)	Use of end product
Piperazine	Scrubber			Gas-washer formulations	
Piperazine	Hardener			Prepolymer for glue	
Piperazine	Raw material	Hydroxyethyl piperazine	Intermediate	Triethylene diamine	
Piperazine	Raw material	N,N'-dimethyl piperazine	Catalyst		Urethane production
Piperazine	Raw material	N-methyl piperazine	Intermediate	Antibiotics (fluoroquinolones); analgesis (clozapine); antiallergy (chlorcyclizine); treatment of male erictile dysfunction (sildenafil)	Human and veterinary medicinal drugs
Piperazine	Raw material		Intermediate	Antihistamines	Human and veterinary medicinal drugs
Piperazine + piperazine salts				Anthelmintics	Human and veterinary medicinal drugs

Humans can be exposed via inhalation, oral and dermal routes. The forms of piperazine which humans can be exposed to via inhalation are as vapour, aerosol of condensed piperazine (mist), airborne solid piperazine or salts of piperazine. Dermal exposure may occur at contact with the pure substance or piperazine salts and at contact with products containing piperazine. However, because of he corrosive properties of pure piperazine (e.g. the base), it is assumed that workers protect themselves against dermal exposure, and thus, no dermal exposure to piperazine base is expected. Humans may be exposed via the oral route via food and drinking water. The following exposure routes for each exposed population are considered to be relevant for this assessment:

Occupational exposure	via inhalation (piperazine and its salts) and via dermal routes (only the piperazine salts)
Consumer end-use	via the oral route via poultry and pigs treated with anthelmintics containing piperazine. Inhalatory and dermal exposure via products such as glues may occur, but is considered negligible.

4.1.2 Occupational exposure

Occupational exposure may occur in industries where piperazine is produced or is used as a raw material as pure piperazine or piperazine salts or as an intermediate. Routes of occupational exposure are assumed mainly to be by inhalation and by dermal contact.

There are several industries in which piperazine is handled, both at the production and at the use of the substance. In some cases the activities may lead to emission of piperazine at the workplace. The exposure of the workers may be similar during similar handling of the substance in the different industries. Therefore the industries have been clustered in similar exposure scenarios based upon the type of process and activity and the possibilities for exposure that relate to that process and activity.

Workers may be exposed to piperazine at work during:

- Production of piperazine free base (flakes and aqueous solution).
- Industrial use of piperazine, piperazine salts and production of piperazine salts.
- Industrial end-use of semi-manufactured products and end-products containing piperazine or piperazine salts.

An overview of the exposure levels for occupational exposure scenarios are given in **Table 4.2**.

Table 4.2 Summary of exposure levels for occupational exposure scenarios

	RWC Conc. Vapour (mg/m^3)	RWC Conc. Dust (mg/m^3)	RWC Derm. Conc. ($mg/cm^2/day$)	Exp Skin Area cm^2	Internal Exp Inhal. (mg/kg/day)	Internal Exp Derm[a] (mg/kg/day)	Total Internal Exp. (mg/kg/day)	Measured Data Inhalation Exp.(mg/m^3)
1A.Production of flakes								
final handling	3.6	5			1.2		1.2	0.02 – 1.2
clean/maintenance	0	5			0.5		0.5	0.07 – 4.4
1B.Production of aq. sol								
final handling	3.6	0			0.5		0.5	0.07 – 4.4
clean/maintenance	72	0			0.5		0.5	
2A.Production of PZ salts								
loading,flakes	3.6	5			1.2		1.2	0.02 – 1.2
loading,aq.sol.	3.6	0			0.5		0.5	
clean/maintenance, flakes	0	5			0.9		0.9	0.2
clean/maintenance,aq.sol.	72	0			0.5		0.5	
final handling	0	2.5	0.5	420	0.9	3	3.4	0.01 – 2.4

Table 4.2 continued overleaf

Table 4.2 continued Summary of exposure levels for occupational exposure scenarios

	RWC Conc. Vapour (mg/m^3)	RWC Conc. dust (mg/m^3)	RWC Derm. Conc. (mg/cm^2/day)	Exp Skin area cm^2	Internal exp . Inhal. (mg/kg/day)	Internal exp . derm[a] (mg/kg/day)	Total Internal exp. (mg/kg/day)	Measured data, Inhalation exp (mg/m^3)
2B.Synthesis processes with PZ								
loading,flakes	3.6	5			1.2		1.2	
loading,aq.sol.	3.6	0			0.5		0.5	
clean/maintenance, flakes	0	5			0.4		0.4	
clean/maintenance,aq.sol.	72	0			0.5		0.5	
2C Formulation with PZ salts								
loading	0	2.5	0.5	420	0.4	3	3.4	
clean/maintenance	0	2.5	0.3	1,300	0.2	2.3	2.5	
3. Use of PZ(flakes) in gas washer								
loading	3.6	5			1.2		1.2	
clean/maintenance	0	5			0.7		0.7	

a Dermal exposure is assumed to be negligible in scenarios where piperazine base is handled, because personal protective equipment (PPE) is assumed to be used because of the corrosive properties of piperazine base.

Based on the physical-chemical information on piperazine and descriptions of the manufacture and formulation/processing of products containing piperazine, the main routes of exposure to piperazine base and salts are as follows:

- The main route of occupational exposure to piperazine base is anticipated to be by inhalation of vapour and solid aerosol. Because of the high pH, of piperazine base, workers should be assumed to wear protective equipment to protect from corrosion, which is thought to also prevent dermal exposure.
- For piperazine salts, exposure is expected via inhalation of solid aerosol and by dermal exposure to piperazine salts as solid dust or dissolved in water (or another solvent).

Assuming that oral exposure is prevented by personal hygienic measures, ingestion of piperazine does not seem to be a relevant route of occupational exposure.

4.1.3 Consumer exposure

Council Regulation (EEC) No. 2377/90, a regulation dealing with the establishment of Maximum Residue Limits for veterinary medicinal products in foodstuffs of animal origin, already covers the use of piperazine in veterinary medicine as an anthelmintic in pigs and poultry (including laying hens). Therefore this use is not further addressed here.

4.1.4 Humans exposed via the environment

Indirect exposure of humans to piperazine via the environment may occur by intake of food, drinking water, and inhalation of air.

4.1.5 Effects assessment

In pigs, piperazine is readily absorbed from the gastrointestinal tract, and the major part of the resorbed compound is excreted as unchanged piperazine during the first 48 hours. The

principal route of excretion of piperazine and its metabolites is via urine, with a minor fraction recovered from faeces (16%). In humans the kinetics of the uptake and excretion of piperazine and its metabolites with urine appear to be roughly similar to that in the pig, and the nature and extent of conversion to metabolites has not been determined.

Piperazine has demonstrated a low acute toxicity (LD_{50} = 1-5 g/kg bw) by the oral, dermal, and subcutaneous route of administration to rodents, whereas adequate inhalation toxicity data have not been found. However, there are findings of EEG (electroencephalogram) changes in 37% of 89 children administrated 90-130 mg/kg piperazine (two doses during one day), corroborated by a proposed GABA (γ-aminobutyric acid) receptor agonism exerted by piperazine. Since clinical symptoms of neurotoxicity may occur after exposure to higher doses, a LOAEL of 110 mg/kg piperazine base for acute neurotoxicity in humans after acute exposure is proposed.

Piperazine, as concentrated aqueous solution, has strongly irritating properties with regard to skin, and should be regarded as corrosive with respect to the eye. Exposure to piperazine and it salts has been demonstrated to cause allergic dermatitis as well as respiratory sensitisation in humans. As shown by the LLNA, piperazine has a sensitising potential in animals. Although piperazine is clearly sensitising, no NOAEL can be set for this effect from the present database.

A NOAEL of 25 mg/kg/day of piperazine for liver toxicity in the beagle dog has been chosen after repeated exposure. A LOAEL of 30 mg/kg/day of piperazine for neurotoxicity is proposed based on documentation of (rare cases) of neurotoxicity from human clinical practice. Neurotoxicity also appears in other species (e.g., rabbits, dogs, cats, tigers, and horses), but not in rodents.

For reproductive effects of piperazine, there is a NOAEL of 125 mg/kg/day for effects on fertility, i.e., reduced pregnancy index, decreased number of implantation sites, and decreased litter sizes in rats. The teratogenic properties have been investigated in rats and rabbits in adequate studies. In rabbit, such effects may be elicited at a dose level that is also toxic to the dam. The LOAEL is 94 mg/kg/day, and the NOAEL 42 mg/kg/day piperazine base (maternal and embryotoxic). In the rat study, there were decreases in body weight of both dams and offspring at the top dose (2,100 mg/kg/day piperazine base), but there were no signs of any malformations.

The genotoxic properties have been investigated both *in vitro* (in the Ames test, in a non-standard study on saccharomyces cervisiae and in Chinese hamster ovary cells) and *in vivo*, in a micronuclei assay on mice, all with negative results. There are no solid indications of a carcinogenic effect of piperazine, neither in animal studies, nor from the investigation on humans. In view of lack of genotoxic action, it appears unlikely that piperazine poses a carcinogenic risk.

4.2 RISK CHARACTERISATION

The key toxicological endpoints for piperazine are skin and eye irritation, corrosion, skin sensitisation, occupational asthma, repeated dose toxicity and reproductive toxicity.

4.2.1 Workers

No NOAEL can be estimated for skin and eye irritation, and for corrosion. Concentrated aqueous solutions of piperazine hydrate have strongly irritating properties with regard to skin, and should be regarded as corrosive with respect to the eye.

Considering that piperazine is already classified with R34, and that workers are assumed to protect themselves with proper PPE against the irritation/corrosion exerted by piperazine base (anhydrate and hexahydrate), **conclusion (ii)** (see Section 5.2.1.1) is warranted.

No NOAEL can be estimated for skin sensitisation. Exposure to piperazine and its salts has been demonstrated to cause allergic dermatitis.

Worker exposure to piperazine salts by the dermal route has been estimated to be up to 0.5 mg/cm^2/day on a skin area of 420 cm^2 during normal work. It is unclear to what extent normal PPE can protect against sensitisation. It is, therefore, concluded that piperazine represents a risk for workers concerning skin sensitisation and **conclusion (iii)** (see Section 5.2.1.1) is warranted.

Exposure to piperazine and its salts has clearly been demonstrated to cause asthma in occupational settings. No NOAEL can be estimated for respiratory sensitisation (asthma). The external worker exposure by inhalation has been estimated to be up to 8.6 mg/m^3 during normal work for an 8-hour day. For short-term exposure (15 minutes), the concentrations may be twice the above mean value.

Based on the high potential for respiratory sensitisation, and the high occupational exposure via inhalation, it is concluded that piperazine represents a risk for workers concerning occupational asthma and **conclusion (iii)** (see Section 5.2.1.1) is warranted. It is unclear to what extent normal PPE can protect against respiratory sensitisation.

A LOAEL for neurotoxicity of 30 mg/kg/day of piperazine base has been set based on the occurrence of cases with neurotoxicity symptoms among patients treated with piperazine for 3-7 days. Thus, this human LOAEL may not be the lowest LOAEL. The case descriptions indicate that the effects are rather serious, although the effects are reversible. **Conclusion (iii)** (see Section 5.2.1.1) is recommended for production of piperazine salts (final handling) and formulation with piperazine salts (loading).

A NOAEL of 125 mg/kg/day has been set for effects on fertility (i.e., reduced pregnancy index, decreased number of implantation sites, and a decreased litter size in rats). Because of the severity of the effect (reduced fertility at a dose twice the NOAEL) **conclusion (iii)** (see Section 5.2.1.1) is recommended for production of piperazine salts (final handling) and formulation with piperazine salts (loading).

4.2.2 Humans exposed via the environment

Regional exposure of adults was estimated to be $2.4 \cdot 10^{-5}$ mg/kg/day, and the highest human exposure via the environment in a local scenario (Use of gas washer formulations) is 0.023 mg/kg/day during infrequent episodes of maintenance of the plants. This scenario is only relevant for acute toxicity, repeated dose toxicity and reproductive toxicity. Based on the calculated MOS's there is no concern for this population.

4.3 HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES)

No concern is recognised for explosivity, flammability and oxidising potential for workers, consumers or humans exposed via the environment.

5 RESULTS

5.1 ENVIRONMENT

5.1.1 Aquatic compartment (incl. sediment)

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

For the local production site C and the local formulation site H the PEC/PNEC ratios are >1. For the industrial use of gas washer formulations, the PEC/PNEC for surface water was >1 at 21 out of 33 local sites. It should be noted that these worst case release calculations are based on TGD defaults for dilution in STP and recipients and, with regard to frequency of release events, information from one company was used for all sites. **Conclusion (iii)** also applies for micro-organisms in the STP for the majority of the local gas washer scenarios.

5.1.2 Terrestrial compartment

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

All PEC/PNEC ratios for the local point sources are below 1. In case the use of piperazine in veterinary medicine increases drastically this has to be reconsidered.

5.1.3 Atmosphere

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

At present, no concern has been raised for the atmospheric compartment.

5.1.4 Secondary poisoning

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

At present, no concern has been raised for secondary poisoning of piperazine.

5.2 HUMAN HEALTH

5.2.1 Human health (toxicity)

5.2.1.1 Workers

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Conclusion (ii) applies to:

- *Acute toxicity*: Although the LD_{50} –levels indicate a relatively low level of oral acute toxicity (LD_{50} 1-5 g/kg bw), signs of neurotoxicity may appear in humans after exposure to lower doses. Based on exposure levels of up to 3.4 mg/kg/day piperazine base and a LOAEL of 110 mg/kg, there is no concern for acute toxicity.
- *Skin and eye irritation, and corrosion:* Concentrated aqueous solutions of piperazine base have corrosive properties with regard to skin, and should be regarded as corrosive with respect to the eye. Considering that piperazine is already classified with R34, and that workers are assumed to protect themselves with proper PPE against the irritation/corrosion exerted by piperazine base (anhydrate and hexahydrate), there should be no further concern.
- *Carcinogenicity:* There seems to be an additional cancer risk due to the formation of N-mononitrosopiperazine (NPZ) from piperazine. It is possible to calculate a hypothetical additional cancer risk posed by NPZ after exposure to piperazine, but the calculation would depend on several assumptions. We conclude that there seems to be an additional cancer risk due to the formation of NPZ from piperazine, and although it is difficult to estimate, it is probably small.

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Conclusion (iii) applies to:

- *Skin sensitisation:* Worker dermal exposure to piperazine salts has been estimated to be up to 0.5 mg/ cm^2/day. Based on the sensitisation potential of piperazine, it is concluded that piperazine represents a risk for all worker scenarios concerning skin sensitisation.
- *Occupational Asthma:* The external worker exposure has been estimated to be up to 8.6 mg/m^3 for an 8-hour day and even higher during peak exposure. Based on the sensitisation potential of piperazine, it is concluded that piperazine and its salts represents a risk for all worker scenarios concerning occupational asthma.
- *Repeated dose toxicity:* The internal worker exposure has been estimated to be 0.5-3.4 mg/kg/day for an 8 hour day exposure. Based on the LOAEL for neurotoxicity in humans of 30 mg/kg/day of piperazine base, it is concluded that piperazine represents a risk for workers (during final handling in production of piperazine salts and during loading in formulation with piperazine salts) concerning repeated dose toxicity.
- *Reproductive toxicity:* The internal worker exposure has been estimated to be 0.5-3.4 mg/kg/day for an 8 hour day. Based on a NOAEL of 125 mg/kg/day, it is concluded that piperazine represents a risk for workers (during final handling in production of piperazine salts and during loading in formulation with piperazine salts) concerning reproductive toxicity.

5.2.1.2 Consumers

Council Regulation (EEC) No. 2377/90, a regulation dealing with the establishment of Maximum Residue Limits for veterinary medicinal products in foodstuffs of animal origin, already covers the use of piperazine in veterinary medicine as an anthelmintic in pigs and poultry (including laying hens). Therefore this use is not further addressed here. Consumer exposure to piperazine via other consumer products is considered negligible.

5.2.1.3 Humans exposed via the environment

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Conclusion (ii) applies to:

- *Acute toxicity, repeated dose toxicity and reproductive toxicity*: Based on the derived MOSs, there is no concern for man exposed via the environment for any of the relevant end-points.

5.2.2 Human health (risks from physico-chemical properties)

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

No concern is recognised for explosivity, flammability and oxidising potential for workers, consumers or humans exposed via the environment.