European Chemicals Bureau

Institute for Health and Consumer Protection

European Chemicals Bureau

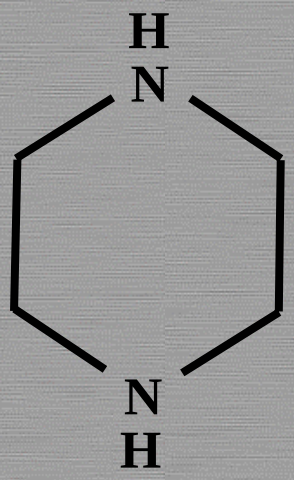
Existing Substances

European Union Risk Assessment Report

CAS No: 110-85-0

EINECS No: 203-808-3

piperazine



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European Union Risk Assessment Report

PIPERAZINE

CAS No: 110-85-0

EINECS No: 203-808-3

RISK ASSESSMENT

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PIPERAZINE

CAS No: 110-85-0

EINECS No: 203-808-3

RISK ASSESSMENT

Final Report, 2005

Sweden

The rapporteur for the risk assessment on piperazine is the National Chemicals Inspectorate, Sweden

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Date of Last Literature Search:	**2003**
Review of report by MS Technical Experts finalised:	**2004**
Final report:	**2005**

Foreword

We are pleased to present this Risk Assessment Report which is the result of in-depth work carried out by experts in one Member State, working in co-operation with their counterparts in the other Member States, the Commission Services, Industry and public interest groups.

The Risk Assessment was carried out in accordance with Council Regulation (EEC) 793/93[1] on the evaluation and control of the risks of "existing" substances. "Existing" substances are chemical substances in use within the European Community before September 1981 and listed in the European Inventory of Existing Commercial Chemical Substances. Regulation 793/93 provides a systematic framework for the evaluation of the risks to human health and the environment of these substances if they are produced or imported into the Community in volumes above 10 t/year.

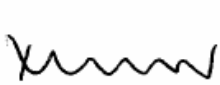
There are four overall stages in the Regulation for reducing the risks: data collection, priority setting, risk assessment and risk reduction. Data provided by Industry are used by Member States and the Commission services to determine the priority of the substances which need to be assessed. For each substance on a priority list, a Member State volunteers to act as "Rapporteur", undertaking the in-depth Risk Assessment and recommending a strategy to limit the risks of exposure to the substance, if necessary.

The methods for carrying out an in-depth Risk Assessment at Community level are laid down in Commission Regulation (EC) 1488/94[2], which is supported by a technical guidance document[3]. Normally, the "Rapporteur" and individual companies producing, importing and/or using the chemicals work closely together to develop a draft Risk Assessment Report, which is then presented at a Meeting of Member State technical experts for endorsement. The Risk Assessment Report is then peer-reviewed by the Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE) which gives its opinion to the European Commission on the quality of the risk assessment.

If a Risk Assessment Report concludes that measures to reduce the risks of exposure to the substances are needed, beyond any measures which may already be in place, the next step in the process is for the "Rapporteur" to develop a proposal for a strategy to limit those risks.

The Risk Assessment Report is also presented to the Organisation for Economic Co-operation and Development as a contribution to the Chapter 19, Agenda 21 goals for evaluating chemicals, agreed at the United Nations Conference on Environment and Development, held in Rio de Janeiro in 1992.

This Risk Assessment improves our knowledge about the risks to human health and the environment from exposure to chemicals. We hope you will agree that the results of this in-depth study and intensive co-operation will make a worthwhile contribution to the Community objective of reducing the overall risks from exposure to chemicals



Roland Schenkel
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Director-General
DG Environment

[1] O.J. No L 084, 05/04/1993 p.0001 – 0075

[2] O.J. No L 161, 29/06/1994 p. 0003 – 0011

[3] Technical Guidance Document, Part I – V, ISBN 92-827-801 [1234]

0 OVERALL RESULTS OF THE RISK ASSESSMENT

CAS No:	110-85-0 Piperazine hexahydrate CAS-No. 142-63-2
EINECS No:	203-808-3
IUPAC Name:	Piperazine

Environment

Aquatic compartment

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.

Terrestrial compartment

Conclusion (ii) There is at present no need for further information and/or testing and 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.

Atmosphere

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

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

Secondary poisoning

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

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

Human health

Human health (toxicity)

Workers

Conclusion (ii) There is at present no need for further information and/or testing and 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. It is concluded 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 (vapour and dust) for an 8-hour day and even higher during peak exposure. Based on the sensitisation potential of piperazine, it is concluded that piperazine 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 and the derived MOSs, 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.

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.

Humans exposed via the environment

Conclusion (ii) There is at present no need for further information and/or testing and 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 humans exposed via the environment for any of the end-points.

Human health – physico-chemical properties

Conclusion (ii) There is at present no need for further information and/or testing and 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.

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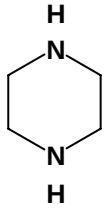
1 GENERAL SUBSTANCE INFORMATION

1.1 IDENTIFICATION OF THE SUBSTANCE

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



1.2 PURITY/IMPURITIES, ADDITIVES

1.2.1 Purity/impurities

The declared purity of the Akzo Nobel 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 (E.Martinsson, Akzo-Nobel, personal communication).

1.2.2 Additives

No additives are reported.

1.3 PHYSICO-CHEMICAL PROPERTIES

1.3.1 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) (BASF, 1997), 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 (see Section 1.3.6).

1.3.2 Melting point

The following melting points for piperazine are given in IUCLID:

- 107-111°C No information on the method used. According to IUCLID, data are well documented and scientifically acceptable (BASF AG, 1997).
- 107.1°C No information on used method. According to IUCLID, the study is well documented and meets generally accepted scientific principles (BASF AG, Analytical Laboratory, 1975).

Values from secondary literature are 106.6°C and 381.78 K.

107°C will be used in this risk assessment report.

The melting point of the hexahydrate is 44-45^{o}C (Trochimowicz et al., 1994).

1.3.3 Boiling point

In IUCLID four values or ranges are given, which are within 146-148.5°C.

The only value from any guideline (DIN 51757) study is 147.7°C (BASF AG, ZET/FE, 1993). There is no documentation. This value is used in this risk assessment.

145-146^{o}C (anhydrous); 125-130^{o}C (hexahydrate) (Trochimowicz et al., 1994).

1.3.4 Density

The density is 1.1 g/cm^3 at 20°C. The method used is DIN 51757 (BASF AG, 1992; Trochimowicz et al., 1994). Values on relative density are from secondary literature only.

1.3.5 Vapour pressure

At 22.5°C the vapour pressure is 0.392 mbar (39.2 Pa) and at 24.2°C 0.44 mbar (44 Pa) (BASF AG, Verfahrenstechnik ZET/FE, 1995). The value given in the Safety Data Sheet from BASF is 15 hPa at 50°C.

0.16 mm Hg (23,2 Pa) at 20°C (Lundberg, 1985).

The value for 24.2°C was used for the EUSES calculation. The model assumes a standard temperature of 25°C; hence the selected value is slightly under-estimated (an extrapolated value for 25°C would be approximately 50 Pa).

1.3.6 Solubility

Piperazine is readily soluble in water and alcohols; insoluble in ether. The water solubility of anhydrous piperazine is reported to be 150 g/l at 20°C. There is no information on the method used to establish the solubility. The pH of piperazine is 12 at a concentration of 150 g/l and 20°C (Calas et al., 1975). This pH (pH 12 at 150 g/l and 20°C) is also reported by (BASF, 1997).

In some of the effect studies different piperazine salts have been used. Therefore information on the solubility of some salts is included below in **Table 1.1**.

Table 1.1 Solubility of piperazine salts, molecular formula and amount of piperazine.

Piperazine salt / CAS No.	Molecular formula (http://chem.sis.nlm.nih.gov/chemidplus/cmplxqry.html)	Solubility in water (Budavari, 1996)	pH of aq. solution	Amount of piperazine in the salt (%) (Plumb 1995)
Adipate 142-88-1 (1:1)	C6-H10-O4.C4-H10-N2	Dissolves slowly. 5.53 g in 100 ml at 20°C.	5.4 (< 5% solution)	37
Citrate 144-29-6 (3:2)	C6-H8-O7.3/2C4-H10-N2	Freely soluble	5-6 (10% solution)	35
Dihydrochloride 142-64-3	C4-H10-N2.2HCl(H2O)	Soluble	3.2 (5% solution)	50-53
Hydrochloride 6094-40-2 (xHCl)	C4-H10-N2.2HCl	Assumingly as soluble as the dihydrochloride	Assumingly, as the dihydrochloride	48
Phosphate 1951-97-9 (xH_3PO_4) 14538-58-8 (1:1)	C4-H10-N2.x-H3-O4-P	- Very slightly soluble in water. - Around 1.5% in water (Eva Martinsson, Akzo Nobel, personal communication)	6.3 (1% solution)	42

1.3.7 Partition coefficient n-octanol/water

The partition coefficient according to a Shake Flask Study log K_{ow} = -1.24 at 25°C, pH 11 **(**BASF AG, Analytical Laboratory, 1989). The study was in principle performed in line with OECD guideline 107[4]. This value will be used in the RAR. Another experimental log K_{ow} = -1.50 at pH 13 is reported as an unpublished result (Hansch et al., 1995).

1.3.8 Flash point

The flash point is reported to be 65°C (BASF AG, 1997).

1.3.9 Autoflammability

There are no data on autoflammability.

1.3.10 Explosivity

There is no information in IUCLID.

Explosion limits in air are given in the Safety Data Sheet: 4-14% (volume) (BASF AG, 1997).

1.3.11 Oxidising properties

Piperazine is not oxidising due to its chemical structure.

[4] OECD Guideline for the Testing of Chemicals. Partition coefficient (n-octanol/water): Shake Flask Method. No 107.

1.3.12 Surface tension

There are no data on surface tension.

1.3.13 Other physico-chemical properties

Reactions of the piperazine base with acids are exothermic (BASF AG, 1997). Piperazine absorbs CO_2 from the atmosphere, being the basis for its use in gas-washers. In acid solution, piperazine is converted to N-mononitrosopiperazine in the presence of nitrite.

1.3.14 Summary

Table 1.2 Data used in the EUSES calculations when applicable.

Melting point	107°C
Boiling point	147.7°C
Density	1.1 g/cm^3 = 1,100 kg/m^3
Vapour pressure	44 Pa at 24.2°C
Solubility in water	150 g/l at 20°C
Partition coefficient: n-octanol/water	log K_{ow} = -1.24 at 25°C

1.4 CLASSIFICATION AND LABELLING

1.4.1 Current classification and labelling

The current classification and labelling according to Directive 67/548/EEC, 22nd ATP (Annex I, index-no 612-057-00-4):

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

1.4.2 Proposed classification and labelling

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

Explanations:

C	Corrosive
R 34	Causes burns
R42/43	May cause sensitisation by inhalation and skin contact
R62	Possible risk of impaired fertility.
R63	Possible risk of harm to the unborn child.
S(1/2)	Keep locked up and out of reach of children.
S22	Do not breathe dust.
S23	Do not breath gas/fumes/vapour/spray *(appropriate wording to be specified by the manufacturer)*
S26	In case of contact with eyes, rinse immediately with plenty of water and seek medical advice.
S36/37/39	Wear suitable protective clothing, gloves and eye/face protection.
S45	In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible).

2 GENERAL INFORMATION ON EXPOSURE

General information on exposure is of importance for estimations of the environmental and human exposure as well as for the risk characterisation and the risk management of the substance. One company claims that due to a joint venture constellation there are in reality only two companies on the European market producing piperazine. Therefore the company is of the opinion that much information on figures shall be put in a confidential annex. Annex C, confidential, describes the situation. More detailed figures are also given in Annex C.

2.1 PRODUCTION

2.1.1 Production, import and export

2.1.2 Tonnage

In 1996/1997 piperazine was produced by 4 plants situated in 4 different EU member states. The United States and Japan are known to produce piperazine and export to the EU. The industrial plants involved are denoted with capital letters.

The tonnage (production + import - export) of piperazine as free base, handled within the EU in 1997 was < 5,000 t. More detailed figures are given in Annex C. The market changes and for example the sales of piperazine salts decreased from less than 60 tonnes 1997 to less than 40 tonnes 2000 in Europe. The figures from 1997 are however used in the report since otherwise it is necessary to ask for new figures and decide another year to be used in all calculations. There is one exception, though, since one company has ceased with the production of piperazine free base in 1999, and that local scenario has been removed from the report.

2.1.3 Production methods

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

2.1.3.1 The ethanol amine based process

Piperazine is synthesised by reaction of ethanolamine with ammonia under high pressure over a catalyst in the presence of hydrogen to produce a mixture of ethylene amines, e.g. piperazine, as well as water as by-product. The ethyleneamines are separated via distillation.

Sometimes this process is integrated with the ethanolamine process. The ethanol amine is synthesised by reaction of ethylene oxide with a large excess of ammonia in a liquid phase to produce a mixture of mono-, di-, and triethanolamines. This reaction takes place in a high-pressure reactor over an ion exchange catalyst. The excess of ammonia is recovered by distillation and recycled to the reactor.

2.1.3.2 The ethylene dichloride based process

Ethylene dichloride is reacted with an excess of ammonia under high pressure and moderate temperature. The resultant ethylene amine hydrochloride solution is neutralised with caustic

soda to form piperazine and other ethylene amines, which are subsequently isolated by distillation. Sodium chloride is formed as a by-product.

2.2 USES

2.2.1 Use pattern

Piperazine is used as such, as salts for different applications or as intermediate in chemical industry. Different applications of piperazine and derivatives are presented in **Table 2.1**.

Table 2.1 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 (chlozapine); 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

2.2.2 Processing as intermediate for chemical industry

A derivative of piperazine (N, N-dimethyl piperazine) is used as polyurethane catalysts in paints/adhesives and in polyurethane foam. Aminoethyl piperazine is used in epoxy hardeners for further processing to paints/adhesives. Piperazine is also used as intermediate in the production of bis- and polyamides. No information is available on quantities, and these use patterns are not included in the risk assessment.

Piperazine, hydroxyethyl-piperazine, aminoethyl-piperazine and N-methylpiperazine (NMP) are also used for pharmaceuticals and further use as drugs for human and veterinary medicine. NMP is used in production of pharmaceuticals for example antibiotics (fluoroquinolones), analgesis (clozapine), and antiallergy (chlorcyclizine). NMP is also used in manufacturing sildenafil as is used in treatment of male erectile dysfunction.

Within the human medicinal area different piperazine derivatives are used as antihistamines. Cetrizinum INN ([2-[4-[Phenyl(4-chlorophenyl)methyl]-1-piperazinyl]ethoxy]acetic acid, chlorcyclizinum INN (1-[phenyl(4-chlorophenyl)methyl]-4-methylpiperazin) cyclizinum INN (1 - diphenylmethyl - 4 - methylpiperazine) and 1 - [phenyl(4 - chlorophenyl)methyl – 4 - (3 -

methylbenzyl)piperazine are listed in Sweden for that purpose (FASS 96, 1996). Cinnarizin is a piperazine derivative ((E)-1-cinnamyl-4-(diphenylmethyl) piperazine), which is an antihistamine for systemic use in the respiratory tract (FASS, 1998). Piperazine is used in the synthesis of the HIV protease inhibitor indinavir ([1(1S,2R),5(S)]-2,3,5-Trideoxy-N-(2,3-dihydro-2-hydroxy-1H-inden-1-yl)-5-[2-[[(1,1-dimethylethyl)-amin]carbonyl]-4-(3-pyridinylmethyl)-1-piperazinyl]-2-(phenylmethyl)-D-erythor-pentonamide) (Rossen et al., 1998). According to de Boer et al. (2001) "1-Aryl-piperazine compounds are, depending on their substituents, selective for certain serotonin receptors and together with their easy availability and their so-called legal status, this group of psychoactive compounds are potential designer drugs-of abuse".

When used as intermediate in the production of derivatives, piperazine is assumed to be totally consumed in the process. Although theoretically possible that a minor part of the derivatives may release piperazine in their further life cycle, this assessment does not consider this possibility.

2.2.2.1 Sales statistics from Sweden for piperazine derivatives used as medicinal drugs.

Apoteket AB follows the sale of medicinal drugs for human and veterinary use in Sweden. The following end products, piperazine derivatives, from **Table 2.2** antibiotics (fluoroquinolones); analgesis (chlozapine); antiallergy (chlorcyclizine); treatment of male erectile dysfunction (sildenafil); and HIV protease inhibitor (indinavir) can be found in different pharmaceutical products, mainly for humans, in Sweden (FASS 96, 1996) (FASS, 1998).

Table 2.2 Sales statistics in Sweden according to Apoteket AB (personal information). Substances where piperazine has been used as a process chemical.

Substance	Mol. weight	% piperazine	1997 kg substance and kg approximated as piperazine	1998 kg substance and kg approximated as piperazine	1999 kg substance and kg approximated as piperazine
Ciprofloxacin	331	26	33,620.8 8,741.4	30,133.5 7,834.7	30,285.1 7,874.1
Enrofloxacin	359	24	177.8 42.7	174.4 41.8	154.0 37.0
Grepafloxacin	359	24	0 0	4.2 1.0	2.7 0.6
Levofloxacin	361	24	0 0	0.3 0.1	5.3 1.3
Norfloxacin	319	27	52,720.9 14,234.6	53,308.6 14,393.3	50,774.5 13,709.1
Ofloxacin	361	24	88.1 21.1	97.5 23.4	100.2 24.0
Trovafloxacin	416	21	0 0	6.8 1.4	19.4 4.1
Fluorquinolones Sum of above as piperazine			22,997.1	22,253.9	21,613.2

Table 2.2 continued overleaf

Table 2.2 continued Sales statistics in Sweden according to Apoteket AB (personal information). Substances where piperazine has been used as a process chemical.

Substance	Mol. weight	% piperazine	1997 kg substance and kg approximated as piperazine	1998 kg substance and kg approximated as piperazine	1999 kg substance and kg approximated as piperazine
Chlozapine	327	26	2,722.0 707.7	2 912.6 757.3	2,839.7 738.3
Cyclizine	266	32	277.8 88.9	313.8 100.4	323.0 103.4
Indinavir	613	14	100.6 14.1	85.7 12.0	61.4 8.6
Sildenafil	718	12	0 0	179.2 21.5	576.3 69.2
Total as piperazine		mean 23%	23,850.5	23,186.9	22,569.7

To extrapolate the above figures for the whole EU for 1997, one way is to relate to the gross national product (G.N.P.) in the different Member States. Based on figures from OECD 1996 the relative scale of G.N.P. for EU would be: 842,773.9 kg as piperazine**.**

Table 2.3 Estimated amount of piperazine sold in different EU Member States, 1997.

Member State	Relative contribution OECD %	Relative contribution EU %	Amount of piperazine (kg)
Austria	1.02	2.56	21,575.0
Belgium	1.24	3.11	26,210.3
Denmark	0.73	1.83	15,422.8
Finland	0.5	1.25	10,534.7
France	7.07	17.71	149,255.3
Germany	11.05	27.69	233,364.0
Greece	0.38	0.95	8,006.4
Ireland	0.24	0.60	5,056.6
Italy	5.94	14.88	125,404.8
Luxembourg	0.1	0.25	2,106.9
Netherlands	1.82	4.56	38,430.5
Portugal	0.45	1.13	9,523.3
Spain	2.86	7.17	60,426.9
Sweden	1.13	2.83	23,850.5 from table above
United Kingdom	5.38	13.48	113,605.9
Total EU	39.91	100	842,773.9

Thus the amount of piperazine used within the EU for synthesis of medical drugs, piperazine derivatives, should be < 1,000 tonnes/year.

2.2.3 Use in gas-washer formulations

Piperazine is used in the formulation of a gas washer liquid. The main formulated part is exported outside EU. During this use the emissions are mainly to the air and are reported to be 3-5 tonnes/year within the EU. The number of plants that are using this gas-washing system is 33 within the EU.

Patents on gas washer applications using piperazine in aqueous solutions for removal of acidic substances, e.g. carbon dioxide or hydrogen sulphide, from gases e.g. natural gas have been published (Wagner et al., 1991).

Gas washing, gas cleaning, or gas absorption, is a standard operation in the chemical industry to separate gases by washing or scrubbing a gas mixture 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 purpose of such scrubbing operations may be; gas purification, product recovery, or production of solutions of gases. Gas washing is usually carried out in vertical counter-current columns. The liquid is fed at the top of the absorber column, whereas the gas mixture enters from the bottom. The absorbed substance is washed out by the dissolving liquid and leaves the absorber at the bottom. The liquid is (often) recovered in a subsequent stripping or desorption operation. This second step is often the reverse of the absorption step.

Releases of constituents of the solvent may take place at the regeneration, mainly as gas or vapour. The flow of the liquid solvent phase is recycled 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 the process water with significant amounts of piperazine are released to waste water.

In Norway a new production plant for liquid natural gas is planned. In the application for releases to the environment there is a description on releases to and from a waste water treatment plant where piperazine is mentioned (Anonymous). The information in the document on the site and the use of piperazine at the site, is too limited for assessing the risks of piperazine releases e.g. no data on releases during cleaning of the washing equipment are given. It is recommended to take into account the outcome of the PEC/PNEC calculations in this RAR (see Section 3.3) concerning existing methodologies for gas washing.

2.2.4 Use as such or as salts in pharmaceuticals; anthelmintics

Piperazine is processed to salts (citrate, dihydrochloride, adipate, phosphate etc.), which are mainly used as active ingredients in pharmaceuticals, e.g. anthelmintics for domestic animals.

Piperazine as such or as different salts (e.g. piperazine citrate) is formulated to human and animal drugs, principally for treatment of intestinal parasites. From piperazine salts, the same ionic species are formed in the environment as from piperazine itself, independent to the originally used compound. Therefore, in the environmental exposure assessment the emissions from the formulation stage of the salts are treated as formulation of piperazine.

Piperazine citrate is used against both large roundworm (*Ascaris lumbricoides*) and pinworm (*Enterobius vermicularis*). A number of substituted piperazine derivatives are active in this respect, but only diethylcarbamazine have found wider clinical use. Piperazine is given orally and causes flaccid paralysis of the parasites due to failure of the musculature to respond to acetylcholin, whereby they are dislodged from the digestive tract but still alive when excreted (Saz and Bueding, 1966; Kirk-Othmer, 1992).

Piperazine is used for treatment of some gastro-intestinal roundworms such as *Toxocara, Toxascaris,* and *Uncinaria* in dogs and cats (Bishop, 1996). In UK piperazine was registered for use at indications of gastro-intestinal roundworms in dogs, cats, and pigeons in 1998 (Bishop, 1998). Piperazine was registered as piperazine, piperazine citrate, piperazine dihydrochloride, piperazine hydrate, and piperazine phosphate.

Piperazine as sulphate is used as a wormer in drinking water for the control of large roundworms (*Ascaridia* spp.) in chickens and turkeys, large roundworms (*Ascaris lumbricoides*) and nodular worms (*Oesophagostomum* spp.) in swine, large roundworms (*Toxikara canis* and *Toxascaris leonina*) in dogs and cats, and large roundworms (*Parascaris equorum*), strongyles (*Strongylus vulgaris*) and small strongyles and pinworms (*Oxyuris equi*) in horses (Bennett, 1993).

Piperazine and its salts, as a γ-aminobutyric acid (GABA)-like substance, induce a reversible flaccid paralysis in the nematode parasites. This is provoked by a hyperpolarisation of the cell membrane followed by suppression of spontaneous spike potentials (EMEA, 2001b). Other uses:

Piperazine is also used as hardener in prepolymer for two-component epoxy glue.

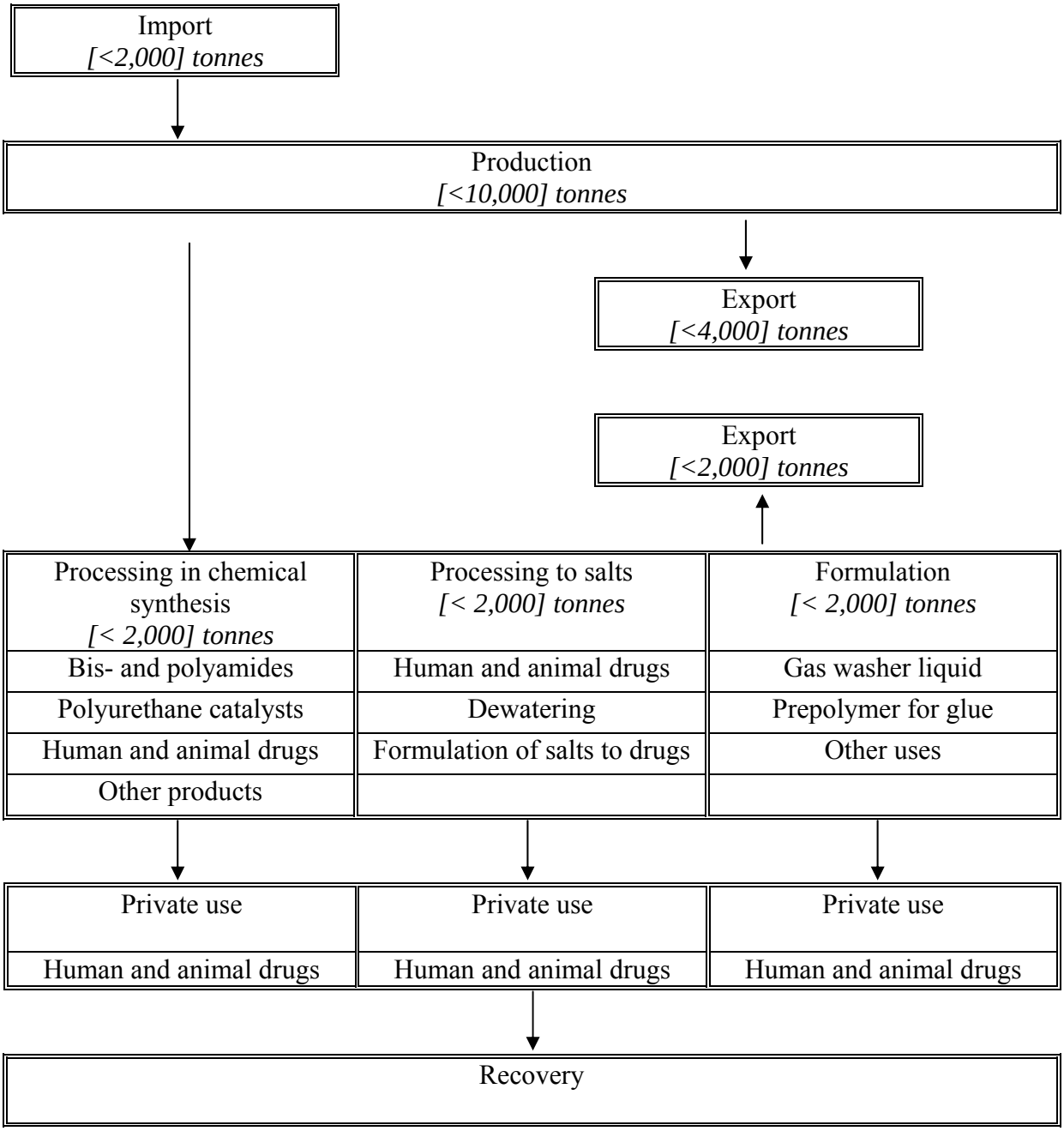
The number of patents, according to US Patent and Trademark Office, containing "piperazine" has increased dramatically from around 2,500 in 1976 to around 7,500 in 2000 (http://164.195.100.11/netahtml/search-bool.html).

Piperazine can be used as corrosion inhibitor, accelerator for curing polychloroprene (Lewis Sr. and R, 1993). The piperazine salt dihydrochloride can be used in the manufacture of fibers and insecticides (American Conference of Governmental Industrial Hygienists Inc., 1993).

2.2.5 Life cycle stages

Piperazine is produced in and imported into the European Union. Some is also exported. Manufacturing of end products containing piperazine involves the life cycle stages formulation, processing, industrial and non-industrial end-use and disposal (see **Figure 2.1**).

Figure 2.1 Life cycle stages of piperazine, 1997.



More detailed information on quantities attributed to different life cycle stages are given in Annex C.

EU industrial use, processing of piperazine as raw material in chemical synthesis as well as formulation of piperazine as such or as salts or other uses, amounted to < 4,000 tonnes/year in 1997. Of the total tonnage for 1997, approximately 75% was specified with regard to use pattern. According to recently submitted figures for 2002, the total production in the EU has increased, but since a larger portion of the production volumes is exported outside the EU, the total tonnage has decreased compared to 1997. For 2002 a larger portion (97%) of the tonnage was specified, but the proportional distribution between different use patterns had not significantly changed. Therefore, the scenarios based on the 1997 figures are still considered to be reasonable. Little information is available on industrial and non-industrial use of end products containing piperazine.

2.3 RELEASES OF PIPERAZINE

2.3.1 Environmental releases and exposure

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

- Production of piperazine based on site-specific information and, where such data is missing; on generic default values from the Technical Guidance Document (TGD).
- Processing of piperazine to salts and processing of piperazine as intermediates based on site-specific information and default values from the TGD.
- Formulation of piperazine as such or as its salts based on site-specific information and default values from the TGD.
- Use of gas washing formulations based on information given by industry.
- Private use of pharmaceuticals with piperazine, its salts and derivatives based on estimated quantities within EU and default release values from the TGD.
- Use of manure from animals treated with piperazine (anthelmintics) as fertiliser on agricultural fields and grassland. Model for the environmental release of veterinary products.

2.3.2 Humans exposed via the environment

Exposure to humans 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

2.3.3 Direct exposures to humans

Limited information on the human exposure to piperazine has been submitted by industry. Occupational exposure has been determined for production of piperazine (flakes and aqueous solution), for the manufacture of piperazine salts, for the industrial use of piperazine and piperazine salts (formulation and processing). Consumer exposure has been estimated for exposure via meat and eggs from livestock treated with anthelmintic pharmaceuticals.

See Section 4.1.1.3 (Occupational exposure) and Section 4.1.1.5 (Consumer exposure).

2.4 CONTROLS ON PIPERAZINE

2.4.1 Transport

Table 2.4 Transport information

Transport information		
Land transport	ADA/RID	Class: 8 Item number/letter: 52c Hazard-no: 80 Substance no.: 2579 UN-No: 2579 Description of the goods: Piperazine (Diethylendiamine)
Inland waterway transport	and/ADNR	Class: 8 Item number/letter: 52c Description of the goods: Piperazine (Diethylendiamine)
Sea transport	IMDG/GGVSee	Class: 8 UN-No: 2579 PG: III EMS: 8-05 MFAG: 320 Marine pollutant: no Proper technical name: Piperazine, solid or solution
Air transport	ICAO/IATA	Class: 8 UN/ID-No.: 2S79 PG: III Proper technical name: Piperazine, solid or solution

Information from (BASF AG, 1997).

2.4.2 Pharmaceuticals

Piperazine is used in human and veterinary medicine products. These products are regulated via Council Directive 75/319/EEC, of 20 May 1975, on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products; and Council Directive 81/851/EEC of 28 September 1981 on the approximation of the laws of the Member States relating to veterinary medicinal products.

2.4.3 Narcotics/abuse-drugs.

Benzylpiperazine has been proposed by the National Institute of Public Health, Sweden, to be classified according to the Swedish regulation (1999:58) on control of certain products dangerous to human health.

2.4.4 Occupational exposure limits

Commission Directive 2000/39/EC (European Commission, 2000) establishes a first list of indicative occupational exposure limit values. The values for piperazine concerning vapour and dust are 0.1 mg/m^3 for 8-hour exposure and 0.3 mg/m^3 for short-term exposure. The list will be implemented in EU member states 31 December 2001.

3 ENVIRONMENT

3.1 ENVIRONMENTAL EXPOSURE

3.1.1 General discussion

Releases of piperazine to the environment are to be expected during the following life cycle stages

- Production;
- processing of piperazine as raw material in the synthesis of derivatives;
- processing of piperazine to salts;
- formulation of the substance, as such or as salts, to human or animal drugs or to other formulations. In the salts, piperazine is still present and the same ionic species are formed in the environment, independent to the originally used compound (piperazine or a salt);
- use of products containing piperazine, its salts or derivatives (human and animal drugs, gas washer formulations, corrosion inhibitors, hardeners for epoxy resins, etc.);
- disposal of piperazine containing products.

3.1.1.1 Release to the environment

There is no information in IUCLID about the potential release of piperazine to the environment. However, some site-specific data are available for production and processing/formulation of piperazine. The table below indicates where information is available and where default values from TGD are used; figures are included in Annex C.

Table 3.1 Summary of available site-specific information.

Site	Life cycle stage	Emission to air	Emission to waste water	Number of days	Effluent flow	Recipient flow
A	Production	x	x	“continuous”	x	x
B	Production	x	x	TGD	x	“sea water” (TGD)
C	Production	TGD	TGD	TGD	TGD	TGD
D	Production, processing and formulation	x (incineration)	x	x	TGD	“estuary” (TGD)
E	Processing	x	x (incineration)	x	TGD	TGD
F	Processing and formulation	x	x (incineration)	TGD	TGD	TGD
G	Processing and formulation	x	x	“continuous”	x	x
H	Formulation	x	TGD	“batchwise” TGD	TGD	TGD

3.1.1.1.1 Release during production and processing/formulation

Site-specific information on the annual release of piperazine to the aquatic environment is available for six point sources. For two production sites, emissions to surface water are

claimed to be zero, since the "effluent" is incinerated. The incinerator is specially designed for this purpose and complete combustion is achieved if oil is used to support the incineration. Information on annual release to air is available for three production sites and four processing sites. The site-specific information regarding release to the environment and details on generic calculations of local environmental concentrations are included in Annex C.

No direct release of piperazine to soil is reported from local point sources, and no significant aerial deposition or exposure via sludge is expected. For the regional and continental scenarios in EUSES, release to soil is based on emission factors from TGD.

3.1.1.1.2 Release during industrial use

Piperazine is reported to be used in gas washing liquid formulations on 33 sites within the EU. The total release to air during this use is reported to be 3-5 tonnes/year. During the process, no release to waste water is reported to occur. However, at intervals of 3-5 years the gas washer plants are rinsed and the process water with significant amounts of piperazine is released to waste water. In total, the yearly emission of piperazine to waste water is 5 tonnes/year in the EU.

A considerable share of the amount of piperazine used in gas washers per year follows the washed gas streams. In the case the washed gas is natural gas, piperazine will be burnt together with the gas. In the case the washed gas is synthesis gas (gas mixture mainly composed of carbon monoxide and hydrogen) piperazine will be chemically destroyed, given the conditions of temperature and pressure in the synthesis processes. Synthesis gas is used in several processes like production of methanol, acetic acid, ethylene glycol, olefins, etc. and for the synthesis of ammonia. Given properties and chemical composition, both natural gas and synthesis gas are distributed and used in fully closed systems, so that no human exposure or releases to the environment occurs. Additional and more detailed information concerning handling, transmission, storage and distribution of natural and synthesis gas are described in Ullmann's Encyclopaedia of Industrial Chemistry (Hammer et al., 2000; Hiller et al., 2000).

3.1.1.1.3 Release during private use

No specific information is available on the release of piperazine following private use. The use of piperazine and its dihydrochloride and citrate salts as active ingredients in human drugs could possibly lead to contamination of surface water. For some piperazine derivative products like sildenafil citrate, piperazine could be released from the molecule during degradation processes in the environment. Wetzstein et al. (1999) have shown that basidiomycetes are capable of degrading ciprofloxacin with piperazine as one of the metabolites. In photolysis experiments ciprofloxacin, enrofloxacin and norfloxacin was not photolysed to piperazine (Burhenne et al., 1999a; 1999b).

The use of piperazine in veterinary medicine would mainly cause release to soil via urine and faeces applied as manure. Assuming that no metabolisation of the substance takes place within the animals, significant local levels of piperazine could be expected in soil after treatment of whole stocks of pigs or chickens. This type of scenario was not described during the assessment of piperazine as veterinary medicine (CVMP, 1999). The release and predicted local concentration in soil were estimated using a model for veterinary products, described by Spaepen et al. (1997). Details on assumptions and results of the calculation are given in section 3.1.4 of this RAR.

3.1.1.1.4 Release from waste

No information is available on release of piperazine from waste. Any contribution of such release of the compound to the environment is not possible to quantify and is not taken into account in the further assessment.

3.1.1.1.5 EUSES calculation

For the regional and continental calculations in EUSES, a simplified use pattern distribution was constructed. Total production, import and export from the EU were based on figures from 1997. Information on the formulation and processing life cycle stages was available for 77% of the total tonnage. A similar use pattern distribution was assumed for the remaining 23% in the EUSES simulation.

Emission factors for regional and continental production, processing and formulation scenarios within EU were derived by summing up the local releases from each site, and division with the total EU tonnage for each life cycle stage. Where available, site-specific information was used. In case two or more life cycle stages took place on one site with only one site-specific release figure, the contribution of each life cycle stage was extrapolated from the generically calculated figures.

For the regional scenario the largest industrial plant for each life cycle stage was assumed situated within one region. Details on the calculations of regional release are given in Annex C of this document. For private use of piperazine and derivatives as pharmaceuticals, regional release was assumed to be 10% of the EU release (TGD default).

One scenario was constructed for the use of piperazine in a gas washer formulation. Specific information on tonnage, total release, and the size and location of each local site was given by industry (Annex C). For the regional scenario, the Member State with the highest total tonnage was regarded as one region, accounting for 24% of the total release in the EU. The resulting regional release to air and waste water was 2.7 and 2.4 t/year, respectively. These figures were used in the EUSES calculations of the predicted regional concentrations in air and surface water.

A private use scenario was constructed for pharmaceuticals. This use pattern includes piperazine used as active ingredient in human drugs, piperazine in salts and piperazine released after degradation of derivatives (only a minor part of the total amount of derivatives are included, since the majority is assumed not to release piperazine).

The simplified use patterns as specified for the EUSES calculations of the environmental regional and continental distribution of piperazine are given in the table below. The fraction of total EU-tonnage for each use pattern can be found in Annex C.

Table 3.2 Simplified use pattern distribution for piperazine as simulated in EUSES

USE PATTERN	LIFE CYCLE STAGE	INDUSTRIAL CATEGORY	MAIN CATEGORY	USE CATEGORY
1	Production	2 Basic chemicals	1c "stored off-site"	55 Others
2 intermediates	Processing	3 Chemicals used in synthesis	III default	33 Intermediates
3 salts	Processing	3 Chemicals used in synthesis	III default	41 Pharmaceuticals/ 55 Others
4 gas washers and others	Formulation	2 Basic chemicals	III default	55 Others
5 piperazine and piperazine salts	Formulation	2 Basic chemicals	III default	41 Pharmaceuticals
6 gas washers	Processing	2 Basic chemicals	III default	55 Others
7 human and medical drugs	Private use	5 Personal/ domestic use	IV wide dispersive use	41 Pharmaceuticals, oral route
8 anthelmintics	Private use, vet. medicine	1 Agricultural chemicals	IV wide dispersive use	41 Pharmaceuticals, oral route

3.1.1.2 Degradation

3.1.1.2.1 Abiotic degradation

Photolysis

The elimination coefficient for photolytical degradation in air was calculated to be $k=1.63 \cdot 10^{-10}$ $cm^3/mol \cdot s$ (half-life 0.8 hours), according to the Atmospheric Oxidation Programme (Meylan and Howard, 1993). Thus, piperazine can be expected to be rapidly photolysed in the atmosphere.

In a recently submitted study (Rouchaud et al., 1978) the photolysis of piperazine in water was investigated. A solution (10 ml) of piperazine in distilled water (100 mg/100 ml) was irradiated at 25-27°C in an open Pyrex glass test-tube (15 mm diameter, 17 cm height, 2 mm thick) at a distance of 20 cm from the ultraviolet lamp. Control samples were incubated in the dark.

After approximately one week of illumination, 65% of the initial piperazine was transformed to glycine (approximately 25%) and three unidentified compounds (approximately 13% each). The half-life time for the parent compound was 5.3 days in the test system. The results from this study indicate a potential for photolytical degradation of piperazine, however, the light conditions were optimised and not relevant for determination of the rate of degradation under natural conditions. In the majority of surface waters, dissolved organic matter and particles makes photolysis processes restricted to the upper zones of the water bodies, and photolysis is generally considered to be of little importance for the degradation of chemicals in the aquatic environment.

Since no environmentally relevant degradation rates are determined, piperazine is considered to be stable towards photolysis in natural water.

Hydrolysis

No studies on hydrolytic degradation of piperazine are available. In a study on the biotic degradation of piperazine (Emtiazi and Knapp, 1994**)** a sterile control (kept in darkness) showed no degradation during the test period, indicating that the compound is persistent to hydrolysis. There is also information on the stability of piperazine under highly acidic and alkaline conditions, respectively, which implies that no hydrolytic degradation takes place (Lightbody and Thomson, 1998). In the absence of standard data on hydrolytical degradation, the conservative assumption that piperazine is hydrolytically stable will be used in the risk assessment.

3.1.1.2.2 Biotic degradation

Ready biodegradability

Study 1: The ready biodegradability of piperazine was investigated in a DOC-Die Away-Test (OECD 301A) (BASF AG, Labor Ökologie, 1993b). The inoculum was from a domestic sewage treatment plant (30 mg/L). The test concentration of piperazine was 34.5 mg/L. Sodium benzoate was used as a reference substance. Duplicate samples were analysed at intervals for 28 days. Test temperature was not reported, pH 7.4. There was no degradation of piperazine observed during the test period, while 96% of the reference substance was eliminated after one day. The study is valid.

Study 2: In another study, according to MITI (I) (OECD 301C) (Chemicals Inspection & Testing Institute Japan, 1992). Activated sludge was used as inoculum (30 mg/L), pH 7. The test concentration was 100 mg/L, and the reference substance used was aniline. After 14 days, 1.4% of the test substance was biodegraded, compared to > 60% of the reference substance. However, the results support the conclusion that the biodegradation of piperazine is slow.

Study 3: The ready biodegradability was also investigated in a Closed Bottle Test (OECD 301D) (van Ginkel, 1990). The inoculum was activated sludge obtained from a domestic wastewater treatment plant; diluted to 2 mg dw/L. The test concentration of piperazine was 2 mg/L, the temperature was not reported, and the pH was 6.9 (at day 28). Sodium acetate was used as reference substance. The test duration was prolonged to 70 days (samples were taken at days 42 and 70). No significant degradation took place during the first 28 days of incubation (90% of the reference substance was degraded at the same time). After 42 and 70 days, 51% and 76% of the original piperazine was degraded. The study is valid.

The results from the studies summarised above indicate that piperazine is not readily biodegradable under aerobic conditions.

Inherent biodegradation

Study 1: The inherent biodegradation of piperazine was studied in a Modified SCAS test (OECD 302A) (van Ginkel and Stroo, 1992), where the conditions are considered to be optimised in favour of the biodegradation of chemical substances. The sludge originated from domestic sewage, and the concentrations of microorganisms (2 g dw/L) were maintained by daily addition of primary settled sewage. The influent concentration of piperazine was 29.7 mg NPOC/L (non-purgeable organic carbon) for a period of 9 weeks. The test was performed under diffuse light at 20-23°C. Phosphate buffer was added six times a week to maintain a constant pH in the SCAS units.

On day one of the study, 47% of the NPOC was dissipated, probably not by biodegradation but dilution of the test solution. Disregarding this initial decrease in the effluent concentration, there was a lag period of approximately 30 days until the microorganisms were acclimatised and a significant biodegradation could be observed. After 7 weeks, > 90% of piperazine was biodegraded. The pH-interval measured within the study was not reported (the figures were mixed up with the temperature values). However, the study is considered to be valid.

Study 2 and 3: In two studies (BASF AG, Labor Ökologie, 1979a, 1993a) performed according to Zahn-Wellens test (OECD 302B), the degradation of piperazine was investigated in adapted sludge from "BASF-Kläranlage" (STP, probably adapted to piperazine) mixed with sludge from a domestic STP.

The test report of one of the studies (BASF AG, Labor Ökologie, 1979a) was scarce. Incomplete information was given about the test conditions and results, no replicate testing was performed, and no reference substance was used. The pH (7.0-8.9) was not adjusted during incubation, as recommended in the OECD Guidelines, above, (max-recommended 8.0). After 16 days, 91% of piperazine was eliminated, based on TOC.

In the other study (BASF AG, Labor Ökologie, 1993a), degradation was observed for 17 days in single samples. A lag phase of 10 days was observed and after 17 days 94% of piperazine was degraded. The reference substance was diethyleneglycole (99% degradation within 14 days). The test pH was adjusted to 7.2 on day 1. At the end of incubation, the pH was determined to be 4.8.

Study 4, 5, 6: Three studies (BASF AG, Labor Ökologie, 1979b, 1980, 1981) claimed to be conducted according to OECD Guidelines 303A (Simulation Test – Aerobic Sewage Treatment: Coupled Unit Test) were performed in activated sludge from domestic STP (not adapted). The results indicate slow degradation of piperazine in non-adapted sludge. In one study, no degradation could be observed after 206 days (BASF AG, Labor Ökologie, 1981); in a second study 2% of piperazine was degraded after 39 days (BASF AG, Labor Ökologie, 1979b). In the third study, around 23% of piperazine was degraded after 40 days (BASF AG, Labor Ökologie, 1980). In all studies, piperazine was poorly eliminated from the water phase.

Results from the studies on inherent degradation indicate that piperazine is inherently biodegradable.

<u>Degradation in water and suspended soil</u>

The capability of microbes in environmental samples (6 surface water sites, 4 sludge sites, and 8 suspended soils/leaf litter/composts) to degrade piperazine and related amines was determined in die-away tests (Emtiazi and Knapp, 1994). 25 ml of water, activated sludge or soil suspensions were added to 50 ml of a sterile solution of the amine in mineral salts medium and 25 ml of sterile distilled water. The final test concentration was 1 mM (corresponding to 86 mg/L of piperazine). When soil was used 40 g (fresh weight) was agitated with 200 ml of water; settled overnight and 25 ml of the supernatant were withdrawn and used as inoculum. The samples were incubated at 27°C. The number of microbes capable of degrading piperazine was determined and the bacteria were isolated and identified. The degradation of amines was monitored spectrophotometrically in the supernatant of centrifuged samples at regular intervals. Additionally, the possible inhibitory effects on the growth of two pseudomonads were investigated at concentrations of amines between 1 and 100 mM (86-8,600 mg/L).

The time for 100% primary degradation of piperazine in surface waters ranged between 39 and 61 days, with a lag period to apparent degradation between 18 and 47 days. In pit tip and dump leachate water, there was no degradation observed in 3 months. The lack of degradation in the leachate water may be explained by the presence of other contaminants, which inhibited piperazine-degrading microorganisms.

In suspended activated sludge, piperazine was completely degraded after 21-26 days, with lag phases of 14-16 days. In samples from humus tanks of a sewage works, the degradation time was 53 days, with 39 days lag period. In suspended soils, the time for 100% primarily degraded was between 24 and 68 days, with lag periods between 15 and 60 days, while in leaf litter and one compost no degradation was observed during 3 months. In general, samples from sites that are likely to have been exposed to pollution of amines show a more rapid degradation rate than samples from sites regarded as unpolluted. Piperazine was concluded to be the most persistent of the tested amines. Piperazine was shown not to inhibit growth of the tested microorganisms. Of the piperazine-degrading bacterial strains isolated, five were *Mycobacterium* sp. and one an *Arthrobacter* sp.

3.1.1.2.3 Summary of degradation studies

Table 3.3 Summary of available data on abiotic and biotic degradation of piperazine

Method	Conditions	Results	Quality of the data	Reference and comments
Photolysis in air	Calculation of degradation in air according to Atmospheric Oxidation Programme	$K = 1.63 \cdot 10^{-10}$ cm³/mol · s (half-life 0.8 hours)	valid	(Meylan and Howard, 1993)
Photolysis in water	Test-tube 15 mm diameter, optimised. Artificial sunlight UV. Conc. 1 g/l Temp. 25-27°C	3 photolytic metabolites; glycine + 2 unknown	no relevant DT_{50} determined	(Rouchaud et al., 1978)
Hydrolysis	Strong acidic and alkaline conditions – not environmental	Stable towards hydrolysis	no standard study	(Lightbody and Thomson, 1998)
Hydrolysis	Dark sterile control in degradation study in sludge. Test conc. 86 mg/L pH 7.0 Temp 27°C.	No degradation	useful information	(Emtiazi and Knapp, 1994)
Ready Biodegradation OECD 301A	Inoculum: domestic sewage (30 mg/L) Test conc. 34.5 mg/L Temp. Not reported pH 7.4	No degradation in 28 days.	valid	(BASF AG, Labor Ökologie, 1993b)
Ready Biodegradation OECD 301C	Inoculum: Test conc. 100 mg/L Temp. pH 7	1.4% degraded after 14 days.	valid with restrictions	(Chemicals Inspection & Testing Institute Japan, 1992)
Ready Biodegradation OECD 301D	Inoculum: domestic activated sludge (2 mg dw/L) Test conc. 2 mg/L Temp. Not reported pH 6.9	28 days: 0% degr 42 days: 51% degr 70 days: 76% degr	valid	(van Ginkel, 1990)

Table 3.3 continued overleaf

Table 3.3 continued Summary of available data on abiotic and biotic degradation of piperazine

Method	Conditions	Results	Quality of the data	Reference and comments
Inherent Biodegradation OECD 302A (SCAS)	Inoculum: domestic sewage (2 g dw/L) Test conc. 29.7 mg/L (NPOC) Temp. 20-23C pH not reported	Lag-phase 30 days, >90% degraded after 49 days.	valid	(van Ginkel and Stroo, 1992)
Inherent Biodegradation OECD 302B (Zahn-Wellens)	Inoculum: BASF+ domestic. Test conc. ? Temp. ? pH 7 - 8.9	Lag phase 3 days. 91% degraded after 16 days.	valid with restrictions	(BASF AG, Labor Ökologie, 1979a) The BASF sludge is probably adapted.
Inherent Biodegradation OECD 302B (Zahn-Wellens)	Inoculum: BASF+domestic Test conc. 373 mg/l Temp. ? pH 6 – 7.2 lag phase, 4.8 – 4.9 degr phase	Lag phase 10 days, 94% degraded after 17 days.	Decrease in pH after the lag phase.	(BASF AG, Labor Ökologie, 1993a)The BASF sludge is probably adapted.
Simulation tests OECD 303A	Inoculum: domestic sludge Test conc not reported Temp not reported pH 7.4 – 9.0	0% degraded after 206 days.	Limited information, only data sheet.	(BASF AG, Labor Ökologie, 1981)
Simulation tests OECD 303A	Inoculum: domestic sludge Test conc. not reported Temp 19-28°C pH not reported	2% degraded after 39 days	Limited information, only data sheet.	(BASF AG, Labor Ökologie, 1979b)
Simulation tests OECD 303A	Inoculum: domestic sludge Test conc. not reported Temp not reported pH not reported	23% degraded after 40 days	Limited information, only data sheet.	(BASF AG, Labor Ökologie, 1980)
Die away test with material from sewage works	Test conc. 86 mg/L Temp 27°C; pH 7.0 Activated sludge Dewsbury Activated sludge Knostrop Activated sludge Owlwood Humus tanks Owlwood	Time to 100% primarily degraded (lag period) 21 (14) days 26 (16) days 21 (14) days 53 (39) days	valid	(Emtiazi and Knapp, 1994)
Degradation in water	Test conc. 86 mg/L Temp 27°C; pH 7.0 Fairburn Ings (lake) Aire and Calder Canal River Aire, Knostrop, Leeds Stream Nr Birkin River Aire (Beal Weir) River Calder Dewsbury Pit tip and dump leachate	Time to 100% primarily degraded (lag period) 48 (36) days 61 (47) days 47 (31) days 53 (18) days 43 (30) days 39 (26) days no degr in 3 months	No standard test procedure. However, useful information for assessment of primary degradation in surface waters.	(Emtiazi and Knapp, 1994)

Table 3.3 continued overleaf

Table 3.3 continued Summary of available data on abiotic and biotic degradation of piperazine

Method	Conditions	Results	Quality of the data	Reference and comments
Degradation in soil	Test conc. 86 mg/L Temp 27°C; pH 7.0 Stable compost (Pudsey) Stream mud – Pudsey Beck Garden soil (Pudsey) Garden soil (J.S. Knapp) Meadow soil, molehill Sykes wood, Leaf litter Troydale Leaf litter Compost	Time to 100% primarily degraded (lag period) 24 (15) days 38 (28) days 42 (30) days 68 (60) days 65 (58) days no degr in 3 months no degr in 3 months no degr in 3 months	No standard test procedure. Soils suspended in water not relevant for assessment of degradation rate in natural soil.	Degradation more rapid in soils from "polluted areas". (Emtiazi and Knapp, 1994)

Piperazine is concluded to be hydrolytically stable. From the calculation on photolysis in air, piperazine can be assumed rapidly degraded in the atmosphere. A potential for photolytical transformation was also seen in an aquatic study. However, in the majority of surface waters, dissolved organic matter and particles makes photolytical processes restricted to the upper zones of the water bodies. At present, since no relevant environmental half-life could be determined, the photolysis rate of piperazine in water is assumed to be zero.

The results from available biodegradation studies indicate that adaptation of microorganisms is an important process for the degradation rate of piperazine in the environment. In non-adapted sludge from domestic sewage treatment plants, the degradation is very slow, with lag-phases of more than 30 days, while in inoculum mixed with sludge from BASF (probably adapted to piperazine) the lag phases were 3-10 days. A study with suspended soils indicated the same pattern – in samples from previously "polluted" areas, the degradation was somewhat faster than in samples unlikely exposed to amines. In surface water, no difference could be seen between polluted and non-polluted site samples.

Since piperazine is an ionising substance, the rate of degradation may be pH-dependent. However, from the available data mostly from studies performed at pH between 6 and 8 (where reported), it is difficult to assess the influence of pH on the degradation rate of piperazine.

No information is available on the primary degradation rate or the degradation pathway of piperazine, since the present studies are aimed at measuring the mineralisation of the substance.

According to TGD, piperazine can be concluded to be "not readily biodegradable" since less than 70% was degraded within 28 days in ready biodegradability tests.

In studies on inherent biodegradability, piperazine was degraded but did not fulfil the specific criteria as given in TGD for when to assume that the substance is degraded in STP. For Zahn-Wellens test, the criteria are "Pass level must be reached within 7 days, log phase no longer than 3 days, below 15% removal before biodegradation occurs". For SCAS tests, no criteria are developed, and a rate constant of 0 shall be used irrespectively if the substance passes the test or not.

For soil and sediment, the degradation rates were extrapolated according to TGD. Biodegradation in surface water was estimated from available simulation data, applying a Q10 factor of 2.2 to reflect a more environmentally relevant temperature.

The table below summarise the extrapolated rates of biodegradation in different environmental compartments according to TGD, together with available simulation data for surface waters. The DT_{50} for surface waters are estimated to be between the first day with observed degradation and the day for 100% primarily degraded. Since the study was performed at 27°C, a Q10 factor of 2.2 was applied in order to reflect degradation under more environmentally relevant temperatures. The available STP simulation data are deficient, and cannot be used for the estimation of the degradation rate for this compartment.

Table 3.4 Degradation rates of piperazine in different environmental compartments. Estimations according to Technical Guidance Document (TGD) and test results

Compartment	Rate constant k	DT50 (d) TGD	DT50 (d) test result	Justification
STP	0 (h^{-1})	Infinite*	-	TGD page 280: "Inherently biodegradable, not fulfilling the specific criteria."
Surface water	0 (h^{-1})	150	64 days at 27°C (worst case of 6 sites, DT_{50} assumed to be between first day of observed degr and day of complete degr, 20 – 64 days). Q10=2.2 results in DT50 140 days at 17°C*.	TGD page 283: "Inherently biodegradable" (Emtiazi and Knapp, 1994)
Soil	-	300*	-	TGD page 284: "Inherently biodegradable". At present no data
Sediment	-	3,000*	-	TGD page 284: "half-life for the sediment compartment will be a factor of ten higher than the half-life in soil"

* These data will be used in the further assessment of the environmental fate of piperazine.

3.1.1.3 Environmental distribution

3.1.1.3.1 Adsorption

No studies are available on the adsorption/desorption of piperazine in STP sludge. In TGD, a QSAR method for calculation of K_{oc} based on the partition coefficient n-octanol/water (K_{ow}) is described. However, the available data on K_{ow} originated from a study performed at pH 11, and cannot be regarded as environmentally relevant. Piperazine is an ionising substance (alkaline) and the adsorption properties are probably pH dependent. For such substances, a correction factor for the partition coefficients at different pH can be calculated as given in Appendix XI in TGD. However, the given equation is only applicable for acids and bases with one pK_a, and cannot be used in this case, since piperazine has two pK_a values. In degradation studies with suspended sludge at pH close to neutral, piperazine was concluded not to adsorb to or partition into solids to any significant extent, but remained in the water phase. Therefore, it is reasonable to believe that the partition coefficients of piperazine between solids and water in STP are close to zero.

Since at neutral pH, piperazine is positively charged, it would theoretically bind to soil particles and humus, which are most commonly negatively charged. Therefore, specific data on soil adsorption/desorption was requested. The study submitted was performed with three different soils (loam, sand and sandy loam) using the batch equilibrium method (OECD Guidelines 106) (Geurts, 2003). The optimal soil solution ratio of 1:5 was used for the final sorption test. Equilibrium was reached after approximately 8 hours. Soil characteristics and resulting sorption data are given in **Table 3.5**.

Table 3.5 Soil characteristics and adsorption data for soils used in the adsorption screening test according to OECD 106. Average of triplicate samples

Soil type	%sand	%silt	%clay	pH	%Org. C	CEC (meq/100g)	Kd (mL/g)
Sandy loam	70	26	4.6	5.7	0.9	5.3	20 (SD 0.69)
Sand	92	5.7	2.5	4.5	2.4	11	15 (SD 1.2)
Loam	35	49	15	7.6	1.4	13	7.9 (SD 0.58)

The results indicate that sorption of piperazine to soil is not correlated to the organic carbon content of the soils.

In calculations for the further assessment of environmental distribution of piperazine, K_{oc} and Kp_{comp} in the STP are assumed to be zero. Consequently, the following distribution constants are calculated in accordance to the TGD equation 10:

$$K_{comp\text{-}water} = Fair_{comp} \cdot K_{air\text{-}water} + Fwater_{comp} + Fsolid_{comp} \cdot Kp_{comp}/1{,}000 \cdot RHOsolid,$$

where $K_{air\text{-}water}$ is the air-water partitioning coefficient ($9.3 \cdot 10^{-6}$, see Section 3.1.1.3.2), $Fair_{comp}$, $Fwater_{comp}$ and $Fsolid_{comp}$ are the fractions of air, water and solids in STP, respectively (see Table 3, page 272 TGD), Kp_{comp} is the solids-water partition coefficient in STP (assumed to be 0), and RHOsolid is the density of the solid phase (see Table 3, page 272 TGD).

For the assessment of the leaching potential of piperazine applied to soil, and for calculation of the predicted no effect concentration for soil dwelling organisms (based on equilibrium partition method), the specific data on sorption in soil will be used. The lowest Kd of 7.9 is used as a worst case.

In the EUSES calculation, K_{ow} is set to the minimum value of -1 and the solubility in water to the maximum value of 100 g/L.

Table 3.6 The assumed constants for each compartment (obtained from TGD) and the calculated partition coefficients are given below

Compartment	$Fair_{comp}$	$Fwater_{comp}$	$Fsolid_{comp}$	RHOsolid	$K_{comp\text{-}water}$
Soil	0.2	0.2	0.6	2,500 kg/m^3	12.1 m^3·m^{-3}
susp. matter	0	0.9	0.1	1,150 kg/m^3	0.9 m^3·m^{-3}
sediment	0	0.8	0.2	1,300 kg/m^3	0.8 m^3·m^{-3}

3.1.1.3.2 Volatilisation

No specific studies on the volatilisation of piperazine are available. The vapour pressure is high, 39 Pa at 22.5°C, indicating a high potential for volatilisation. The Henry's law constant

at 20 - 25°C is approximately $2.2 \cdot 10^{-2}$ Pa · m^3/mol. This value indicates that, due to the high solubility of the substance in water, despite the high vapour pressure, the potential for evaporation from aquatic surfaces is moderate.

From the Henry's law constant, the partition coefficient between air and water is calculated with the equation (TGD equation 8):

$$K_{air\ -\ water} = \frac{HENRY}{R \cdot TEMP}$$, where R is the gas constant (8.314).

The resulting partition coefficient $K_{air\text{-}water} = 9.3 \cdot 10^{-6}$.

3.1.1.3.3 Bioaccumulation

The very low partition coefficient n-octanol/water (log K_{ow} = -1.24 at 25°C, pH 11) indicates that the potential for bioaccumulation is low, even if the pH of the test solution is not environmentally relevant. The results from a study of the bioaccumulation in *Cyprinus carpio* (OECD 305C) support this conclusion. The bioaccumulation was investigated during 42 days at 25°C (pH not reported), in two test concentrations, 0.1 and 1.0 mg piperazine/L. BCF was determined to be 0.9 at the lower concentration, <3.9 at the higher concentration. Thus, bioaccumulation is not considered to be of major importance for piperazine.

3.1.1.3.4 Summary of environmental distribution

Table 3.7 Summary of available data on the environmental distribution of piperazine

Method	Conditions	Results	Quality of the data	Reference
Partition coefficient n-octanol/water (log K_{ow})	Temp 25°C pH 11.	Log K_{ow} = -1.24	The test system was not buffered. The pH was not environmentally relevant.	(BASF AG, Department Toxicology, 1980)
Adsorption in soil	In accordance with OECD 106	K_d 7.9 – 20 in three soils.	Valid for the soil compartment.	(Geurts, 2003)
Other data: comment in STP simulation studies		"the substance was poorly eliminated from the water phase"	Useful information for sorption in STP.	(BASF AG, Labor Ökologie, 1979a, 1993a)
Other data: comment in degradation study with suspended solids	Test conc 86 mg/L Temp 27°C pH 7.0	"…remained in aqueous solution and did not adsorb to or partition into solids to any significant extent"	Useful information for sorption in STP.	(Emtiazi and Knapp, 1994)
Volatilisation	Vapour pressure at 24°C Henry's law constant $K_{air\text{-}water}$	39 Pa $2.2 \cdot 10^{-2}$ Pa · m^3/mol $9.3 \cdot 10^{-6}$	Calculated values.	(BASF AG, Department toxicology, 1964)
Bioaccumulation		BCF 0.9-<3.9	Valid	(Chemicals Inspection & Testing Institute Japan, 1992)

3.1.2 Aquatic compartment

3.1.2.1 Predicted environmental concentrations (PEC) in the aquatic compartment (including sediment and groundwater)

3.1.2.1.1 PEC local

Local concentrations are calculated based on information submitted by industry and, where information is missing, on generic default values given in TGD. More detailed input of the calculations is reported in Annex C.

Distribution in the STP is estimated using SIMPLETREAT, Appendix II in TGD (log K_{ow}, log H, biodegradability):

Henry's law constant: $$H = \frac{\text{molw.} \cdot \text{vap. press}}{\text{water solubility}}$$

H = 0.022 Pa · m^3/mol

log H = -1.65

log K_{ow} = almost 0 (estimated; in the modified SIMPLETREAT model in Appendix II of the TGD the lowest possible log K_{ow} is 0)

Air	0%
Water	100%
Sludge	0%
Removal	0%

According to the generic scenario given in TGD, the local concentration in surface water, $Clocal_{water,}$ is calculated as follows:

$$Clocal, water = \frac{Clocal, eff}{1 + (Kp, susp \cdot SUSPwater \cdot 1.0E - 06)} \cdot D$$

(3) (1) (2)

(1) Since Kp_{susp} is set to 0, $Clocal_{water} = \frac{Clocal, eff}{D}$

(2) The dilution factor D = 10 (according to TGD). In cases where such information is reported for the specific local scenarios, dilution is based on the flow rate of the receiving water body.

(3) The concentration of the chemical in the STP-effluent;

Since the fraction of emission directed to the water by STP (Fstp,water = 100%) (SIMPLETREAT), and no elimination is expected in the STP, $Clocal_{,eff}$ is set equal to $Clocal_{inf}$, the concentration in the untreated waste water:

$$Clocal, \text{inf} = \frac{Elocal, water \cdot 1.0E + 06}{EFFLUENTstp} \text{ (mg/l)}$$

The effluent discharge of the STP:

$EFFLUENTstp = capacity, stp \cdot WWinhab = 2.0E + 06$ (TGD default)

The predicted local concentrations in sediment are calculated according to Equation 35 in TGD, page 304:

$$PEClocal, sed = \frac{Ksusp, water}{RHOsusp} \cdot PEClocal, water \cdot 1000$$

RHO_{susp} = 1,150 kg/m^3
$K_{suspH2O}$ = 0.9 m^3/m^3
$PEC_{local,sed}$ = 0.78 $PEC_{local,\ water}$ mg/kg w.w.

To the calculated local concentration of the substance is added the regional concentration from the EUSES simulation:

$PEClocal_{surface\ water} = Clocal_{surface\ water} + PECregional_{surface\ water}$

The resulting values for $PEClocal_{surface\ water}$ and the corresponding $PEClocal_{sediment}$ for each production/processing site are used in the risk characterisation and reported in the **Table 3.8**.

Table 3.8 Calculated local concentrations (PEClocal) of piperazine in surface water and sediment for known industrial sites. Concentrations during emission episodes and annual mean for surface water, annual mean for sediment

Site	Life cycle stage	PEClocal					
		During emission		Annual mean		Annual mean	
		Surface water (mg/L)		Surface water (mg/L)		Sediment (mg/kg ww)	
		Site spec.	Generic	Site spec.	Generic	Site spec.	Generic
A	Production	0.002*	0.008	0.001*	0.006	0.002*	0.006
B	Production	0.001*	1.3	0*	1.1	0.001*	0.83
C	Production	n.r.	1.5*	n.r.	0.05*	n.r.	1.2*
D	Production / processing / formulation	0.2*	0.91	0.17*	0.78	0.16*	0.71
E	Processing	0.001*	0.29	0	0.18	0.001*	0.23
F	Processing / formulation	0.001*	2.6	0*	0.94	0.001*	2.0
G	Processing / formulation	0.002*	0.002	0.001*	0.001	0.002*	0.002
H	Formulation	n.r.	4.9*	n.r.	0.24*	n.r.	3.8*

n.r. No information submitted
* Figures that are used in the risk assessment.

Additionally, local releases to waste waters are expected from the industrial use of gas washers and from private use of pharmaceuticals (humans). These local scenarios are based on generic default values in TGD and are included in the EUSES calculation. The resulting $PEClocal_{surface\ waters}$ are given in the table below. The locations of the gas washer plants related to rivers are unknown, why further refinement of the dilution factor is not possible.

Table 3.9 Calculated local concentrations (PEClocal) of piperazine in surface water and sediment for local gas washer sites (n = 33) and private use of pharmaceuticals. Concentrations during emission episodes and annual mean for surface water, annual mean for sediment

Life cycle stage	PEClocal		
	During emission	Annual mean	Annual mean
	Surface water (mg/L)	Surface water (mg/L)	Sediment (mg/kg ww)
Industrial use of gas washers	0.02 - 29	0.0 – 0.08	0.01 - 23
Private use of pharmaceuticals	0.002	0.002	0.002

For each gas washer site, see Annex C.

It should be noted that these worst case calculations are based on TGD defaults for dilution in STP and recipients. Proposals have been made to use the Emission Scenario Document IC-3 in TGD together with the estimated release figures for each site. However, the Emission Scenario Document IC-3 is designed for HPV intermediates, and so far the rapporteur has no data supporting that the assumptions on dilution in the recipients given in that document are realistic and applicable for gas washer sites.

The release figures for the sites were determined assuming that the release is proportional to the amounts of washed gas. The rapporteur believes that there might be an uncertainty in this assumption. There may also an uncertainty in the assumption of the frequency of the releases at each site, which is based on specific information from one company.

3.1.2.1.2 PECregional and continental for surface water and sediment

The regional and continental concentrations of piperazine are calculated by EUSES on the basis of the local releases from production, processing and formulation as reported in Annex C. Diffuse emissions from private use of pharmaceutical products containing piperazine, its salts or derivatives are not known. Some piperazine derivatives, e.g. sildenafil citrate, may release piperazine from the molecule during degradation processes in the environment. Since sufficient information is not available, the quantities for this EUSES scenario are roughly estimated to 500 tonnes/year of which a minor part represents derivatives.

Model parameters for the regional and continental models in EUSES (from TGD) are given below.

Parameters	Value
area of the regional system	40,000 km^2
area of the continental system	3,560,000 km^2
area fraction of water	0.03
depth of water	3 m
residence time of water	40 days

Piperazine released via wastewater is assumed to be evenly distributed in the surface water compartment and to remain in the aqueous phase. The degradation half-life of piperazine is assumed to be 140 days in surface water.

$PECregional_{surface\ water}$ is calculated to be 0.59 µg/l.
$PECcontinental_{surface\ water}$ is calculated to be 0.04 µg/l.

The regional and continental concentrations in sediment are calculated with the equilibrium partitioning method:

$PECregional_{sediment}$ is calculated to be 0.35 µg/kg ww.
$PECcontinental_{sediment}$ is calculated to be 0.02 µg/kg ww.

3.1.2.2 Measured levels in the aquatic compartment (including sediment and biota)

Data on measured release levels in recipients are submitted for three local point sources (Annex C). However, no supporting information is given for the evaluation of representativity, reliability and relevance of the measured data. This information gives lower PECs for all local sites.

3.1.2.3 PEC for STP

Local concentrations in STP are calculated based on the information submitted by Industry and, where information is missing the calculations are based on generic default values given in TGD. More detailed data information for the calculations is given in Annex C.

As stated in Section 3.1.2.1.1 PEC local, $C_{local,eff}$ is set equal to $C_{local,inf}$, thus:

$PEC_{STP} = C_{local,inf} = C_{local,eff}$

Table 3.10 Calculated PEClocal for STP for known industrial sites and for use patterns 6-8, for which there are no known specific local sites available

Site	Life cycle stage / use pattern	PEClocal (mg/l)	Comment
A	Production	0.12	Site specific
B	Production	0.002	Site specific
C	Production	15	Site specific
D	Production/processing/formulation	2.0	Generic local processing
E	Processing	2.9	Site specific
F	Processing/formulation	2.6	Site specific
G	Processing/formulation	0.001	Generic local formulation
H	Formulation	0.00005	Site specific
Gas washer	6 Processing	14.5 – 15,000	Generic local EUSES for 30 sites, site specific for 3 sites.
Pharmaceuticals	7 Private use	0.007	Generic local EUSES

3.1.3 Atmosphere

3.1.3.1 Predicted environmental concentrations (PEC) in air

The main sources of piperazine to the atmosphere are direct emissions from local production and processing sites. Volatilisation from STP is probably of little importance (100% partitioned to water, SIMPLETREAT). Since the compound is assumed to be rapidly photolysed under influence of sunlight (photolytical half-life in air calculated to be 0.8 hours)

only local concentrations are expected. The expected concentration of piperazine adjacent to specific production and processing sites is calculated according to TGD Section 2.3.8.2:

$Clocal_{air} = Elocal_{air} \cdot Cstd_{air}$,

where $Cstd_{air}$ is the concentration in air at a source strength of 1 kg/day, or 0.000278 mg/m^3.

For each local site, generic and site specific concentration in air were calculated according to TGD and based on information given by industry. Detailed information on input to the calculations is given in Appendix A – I of Annex C. The resulting figures to the calculated local concentration of the substance is added the regional concentration from the EUSES simulation:

$PEClocal_{air} = Clocal_{air} + PECregional_{air}$

The resulting values for $PEClocal_{air}$ for each production/processing site are given in **Table 3.11**. Figures used in the risk characterisation are marked with *.

Table 3.11 Calculated local concentrations (PEClocal) of piperazine in air. Concentrations during emission episodes and annual mean.

Site	Life cycle stage	$Clocal_{air}$ (µg/m^3)			
		During emission		Annual mean	
		Site specific	Generic	Site specific	Generic
A	Production	0.0*	0.19	0.0*	0.16
B	Production	0.11*	0.24	0.09*	0.20
C	Production	n.r.	0.28*	n.r.	0.011*
D	Production / processing / formulation	0.0*	0.55	0.0*	0.54
E	Processing	0.0*	0.0	0.0	0.0
F	Processing / formulation	0.0*	3.9	0.0*	3.2
G	Processing / formulation	0.58*	3.6	0.52*	3.0
H	Formulation	n.r.	1.9*	n.r.	0.008*

n.r. No information submitted
* Figures used in the risk assessment

Local emissions of piperazine to air are also expected from the industrial use of gas washer formulations (33 sites within EU). For the regional assessment, the MS with the highest tonnage was regarded as one region, accounting for 24% of the EU release.

Regional and continental PECair are calculated by EUSES based on model parameters as given in TGD:

Parameters	Value
area of the regional system	40,000 km^2
area of the continental system	3.560,000 km^2
atmospheric mixing height	1,000 m
wind speed	3 m/s
residence time of air	0.7 days

$PECregional_{air}$ is calculated to be $9.5 \cdot 10^{-6}$ µg/m^3.

PECcontinental$_{air}$ is calculated to be $3.0 \cdot 10^{-7}$ µg/m^3.

3.1.3.2 Measured levels in air

Data on measured release levels in air are submitted for five local point sources (see Annex C). However, there is no supporting information given for the evaluation of representativity, reliability and relevance of the measured data.

3.1.4 Terrestrial compartment

3.1.4.1 Predicted environmental concentrations (PEC) in soil

No direct emissions of piperazine to soil are expected at the local industrial sites. The major exposure routes of chemicals to the soil compartment are via sludge application or atmospheric deposition. However, since piperazine is shown not to adsorb to sludge in STP (100% partitioned to the water phase, SIMPLETREAT) and due to the rapid photolysis in air (DT_{50} 0.8 hours), these distribution routes are probably of low significance.

An exception from the low significance of sludge application for the predicted concentrations in soil might be release of piperazine salts that dissolve slowly in water (for example piperazine-adipate and piperazine-phosphate, see **Table 1.1**). In STP, these salts would stay in the solid phase, and consequently contribute to exposure of the soil compartment via sludge application. However, in the available information from industry, there are no data on the amounts of these piperazine salts that are used within the EU, and no quantitative exposure assessment is possible.

A possible route of exposure for soil is via the use of piperazine as an anthelmintic for domestic animals. Significant local levels of piperazine could be expected in soil after treatment of whole stocks of pigs or chickens.

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 described by Spaepen et al. (1997). The model was slightly modified to be consistent with the sludge scenario of TGD; the soil bulk density was set to 1,700 kg/m^3 (instead of 1,500 kg/m^3) and the mixing depth was set to 0.1 m for grassland and 0.2 m for agricultural soil. Further, the concentrations were given as time weighted average over 30 days for the risk assessment for the terrestrial ecosystem, and over 180 days for agricultural soil with crops for human consumption and grassland soil for exposure of grazing cattle.

From the different scenarios described in the model, treatments of chicken and piglets were selected to represent the worst case with regard to annual amount of piperazine used related to the nitrogen concentration in manure.

Assumptions:

Dose	32 mg piperazine/kg bw given in each of 2 successive feedings or in drinking water for 2 days.	oral, 110 mg piperazine/kg bw, one dose per animal

Metabolism	42% of the dose was recovered as unchanged piperazine in excreta after 24 hours (total residues 70% of the dose).	38% of the dose was recovered as unchanged piperazine in urine after 24 hours (total residues 46% of the dose).
Animal type	Broiler chicken, 1.3 kg bw.	Piglets, 20 kg bw.
Number of animals per year per place	9	6
Amount of manure per year per place	37.2 kg	754 kg
Resulting yearly mean concentration of piperazine in manure	8.4 mg/kg	6.7 mg/kg
Amount of N per place per year	0.21 kg N/place/year	3.35 kg N/place/year
Resulting concentration of N in manure	0.0056 kg N/kg manure	0.0044 kg N/kg manure
"Typical" amount of N applied to arable/grass/maize crops in the EU	170 kg N/ha/year	170 kg N/ha/year
Resulting manuring rate	30,357 kg manure/ha/year	38 263 kg manure/ha/year
Amount of PIP per hectare	256 g piperazine/ha	255 g piperazine/ha
Mixing depth of soil	0.1 m for grassland, 0.2 m for agricultural land (TGD)	0.1 m for grassland, 0.2 m for agricultural land (TGD)
Density of soil	1,700 kg/m^3 (TGD)	1,700 kg/m^3 (TGD)
Resulting initial PECsoil	0.15 mg/kg dw for grassland, 0.076 mg/kg dw for agricultural soil	0.15 mg/kg dw for grassland, 0.076 mg/kg dw for agricultural soil
Degradation rate in soil	300 days	300 days
Averaging time for risk assessment for terrestrial ecosystems	30 days	30 days
Averaging time for agricultural soil with crops for human consumption and grassland soil for exposure of grazing cattle	180 days	180 days
Resulting time weighted	0.14 mg/kg dw for grassland,	0.14 mg/kg dw for grassland,

average PEC for terrestrial ecosystems	0.07 mg/kg dw for agricultural soil (0.12 and 0.06 mg/kg ww)	0.07 mg/kg dw for agricultural soil (0.12 and 0.06 mg/kg ww)
Resulting time weighted average PEC for human exposure	0.10 mg/kg dw for grassland, 0.05 mg/kg dw for agricultural soil (0.09 and 0.04 mg/kg ww)	0.10 mg/kg dw for grassland, 0.05mg/kg dw for agricultural soil (0.09 and 0.04 mg/kg ww)

The assumptions described above can be considered as worst case with regard to: treatment of all animals, no degradation in manure, but not worst case with regard to: Yearly mean concentration in manure, instead of peaks 6 times per year. Realistic assumption that the manure is mixed before spreading on land. The typical manuring rate was set to 170 kg N/ha/year as recommended by the model, although the worst case is 350-600 kg N/ha/year in Italy. The value of 0.12 mg/kg ww is taken forward to the risk characterisation as PEClocal for agricultural soil.

The values for regional and continental PECsoil are calculated generically by EUSES based on generic emission factors and model parameters as given in TGD:

Parameters	Value
area of the regional system	40,000 km^2
area of the continental system	3,560,000 km^2
area fraction of natural soil	0.60
area fraction of agricultural soil	0.27
area fraction of industrial/urban soil	0.10
mixing depth of natural soil	0.05 m
mixing depth of agricultural soil	0.2 m
mixing depth of industrial/urban soil	0.05 m

$PECregional_{natural\ soil}$ is calculated to be $2.0 \cdot 10^{-4}$ µg/kg ww.
$PECregional_{agricultural\ soil}$ is calculated to be $2.0 \cdot 10^{-4}$ µg/kg ww.
$PECregional_{ind/urb.soil}$ is calculated to be $2.0 \cdot 10^{-4}$ µg/kg ww.
$PECcontinental_{natural\ soil}$ is calculated to be $6.5 \cdot 10^{-6}$ µg/kg ww.
$PECcontinental_{agricultural\ soil}$ is calculated to be $6.3 \cdot 10^{-6}$ µg/kg ww.
$PECcontinental_{ind/urb\ soil}$ is calculated to be $6.5 \cdot 10^{-6}$ µg/kg ww.

3.1.4.1.1 Calculation of PEC for groundwater

The predicted concentration of piperazine in groundwater is calculated from PEC_{soil} as given in Section 2.3.8.6 of TGD. The most important exposure route to groundwater is via the use of piperazine as anthelmintics in domestic animals. The predicted local concentration in groundwater is indicated by the concentration in the soil pore water by the equation:

$$PEClocal_{soil,\ porew} = \frac{PEClocal_{soil} \cdot RHO_{soil}}{K_{soil\ -\ water} \cdot 1000}$$

where $PEClocal_{soil}$ is 0.10 mg/kg dw for grassland and 0.05 for agricultural soil, RHOsoil is 1,700 kg/m^3, Ksoil-water 8.3 m^3/m^3 (see Section 3.1.1.3.1).

The resulting local concentrations in groundwater are 0.020 and 0.010 mg/l, under grassland and agricultural soil, respectively. These values must be regarded as worst-case estimations, since the dilution/loss of piperazine with depth is not taken into account. The data will be used in the assessment of human exposure via the environment.

Regional and continental PEC for groundwater is calculated by EUSES based on PEC for agricultural soil according to TGD:

PECregional $_{gw}$ is calculated to be $1.7 \cdot 10^{-3}$ µg/l.
PECcontinental$_{gw}$ is calculated to be $5.2 \cdot 10^{-5}$ µg/l.

3.1.4.2 Measured levels in soil and groundwater

No data are available on measured levels of piperazine in soil or groundwater.

3.1.5 Non compartment specific exposure relevant to the food chain

3.1.5.1 Predicted environmental concentrations (PEC) in biota

Due to the low potential for bioaccumulation of piperazine (BCF=0.9 – <3.9), concentration levels in biota can be expected to be close to the levels in the surrounding environment.

3.1.5.2 Measured levels in biota

No data are available on measured levels of piperazine in biota.

3.2 EFFECTS ASSESSMENT: HAZARD IDENTIFICATION AND DOSE (CONCENTRATION) - RESPONSE (EFFECT) ASSESSMENT

3.2.1 Aquatic compartment

3.2.1.1 Toxicity to micro-organisms

The inhibition of cell multiplication of Pseudomonas putida was investigated during 18 hours in a study generally in accordance with an ISO Guideline (van Ginkel, 1989). The nominal test concentrations of piperazine were 62.5, 125, 250, 500 and 1,000 mg/L. Test temperature was 25°C, pH was adjusted to neutral by means of titration with H_2SO_4. Cell density was determined photometrically in single cultures at the beginning of the incubation and after 18 hours.

No effect on cell multiplication was observed in any of the tested concentrations compared to the controls. NOEC was determined to be >1,000 mg/L (nominal concentration).

The respiration inhibition of nitrifying bacteria was studied in a two hours study (Balk and Meuwsen, 1989c). No guidelines were referred to. The nominal test concentrations were 410, 750 and 1,350 mg/L. The test temperature was 20°C, and the pH was kept neutral with HCl. The respiration was measured in single samples as the concentration of dissolved oxygen in the bacterial suspension by means of an open respirometer. EC50 was determined by probit analysis to be 633 mg/L (95% C.L. 55 – 1,210 mg/L). At the lowest exposure concentration, inhibition was 40% compared to the control. EC10 was extrapolated to be 74 mg/L. During the two hours of the study, respiration was inhibited at all test concentrations. In case of longer exposure periods, which would allow adaptation of the microorganisms it is possible that the respiration rate would recover to some extent. However, the results of this study indicate that piperazine is inhibiting the respiration of nitrifying bacteria.

An activated sludge respiration inhibition test was performed according to EEC Guidelines (OECD 209?) (van Ginkel and Stroo, 1989). Homogenised sludge (0.46 g dw/L) was incubated at 20°C and pH 7.4-7.8 for 30 minutes with nominal test concentrations of 20, 60, 180, 540 and 1,620 mg/L plus control. The oxygen depletion was measured in single samples using an oxygen electrode. At the highest test concentration, respiration inhibition was 16% compared to the control. NOEC was determined to be 540 mg/L. These results will be used for the calculation of PNECstp.

3.2.1.2 Toxicity to algae

The toxicity of piperazine (purity 99%) to *Selenastrum capricornutum* was investigated in a 72 hour growth inhibition test according to OECD Guidelines 201 (van Ginkel et al., 1990). The test was performed in triplicate with the nominal test concentrations 10, 31, 98, 313 and 1,000 mg/L. The test temperature was 22.5-23°C and pH between 6.9 and 7.9. The cell concentrations were determined spectrophotometrically at the beginning of incubation and after 24, 48 and 72 hours.

No effects on algal growth rate or biomass were seen in any of the tested concentrations compared to the controls. NOEC was determined to be >1,000 mg/L (nominal concentration).

3.2.1.3 Toxicity to aquatic invertebrates

The acute toxicity of piperazine (purity 99.9%) to *Daphnia magna* was investigated in a 48-hour static immobilisation test according to OECD Guidelines 202 (Balk and Meuwsen, 1989a). The test was performed with four replicates of five daphnids each. The nominal test concentrations were 18, 32, 56, 100, 180 and 320 mg/L. The test temperature was 19.5-20.5°C, pH of the test medium was neutralised to 7.0-7.3. The number of immobilised animals was observed after 24 and 48 hours. The EC50 was determined by probit-analysis.

The 48 hours EC50 was determined to be 21 mg/L, with a 95% confidence interval of 13-34 mg/L, based on nominal concentrations.

3.2.1.4 Toxicity to fish

The toxicity of piperazine (purity 99%) to guppy *Poecilia reticulata* was investigated in a 96 hour semi-static test according to OECD Guidelines 203 (Balk and Meuwsen, 1989b). The test medium was renewed after 48 hours. The nominal test concentrations were 180, 320, 560, 1,000 and 1,800 mg/L. Test temperature was 22.3-23°C, pH of the test medium was neutralised to 7.0-7.3. Observations of mortality and sublethal effects among the fish (10 per test concentration) were performed at daily intervals during the test.

No mortality occurred in any of the test concentrations, and LC50 could be determined to be >1,800 mg/L. At the highest test concentration, 3 fishes were noted to be "unhealthy" after 96 hours.

3.2.1.5 Chronic toxicity

The long term toxicity of piperazine to *Daphnia magna* was investigated in a 21 day semi-static reproduction study according to OECD Guidelines 211 (Thomas et al., 2002). Nominal test concentrations were 0, 3.1, 6.25, 12.5, 25 and 50 mg/L. Ten vessels per parallel, with one daphnid per vessel, were tested at each test concentration and a control. The daphnids were fed with *Chlorella vulgaris*. Test temperature was 19.4-23.4C, and pH was 7.3-8.4 (adjusted with 1M HCl). Immobilisation of parent daphnids was checked every day of the test. The day of brood release and the number of living and dead neonates per brood or abortions and other abnormal observations were noted. At the end of the test, length and weight of all surviving parent animals were recorded.

The 21 days NOEC was determined to be 12.5 mg/L (nominal), based on immobile neonates at day 15 in two vessels at 25 mg/L. Measured concentrations were 90-105% of the nominal values. The study is considered to be valid.

3.2.1.6 Predicted no effect concentration (PNEC) for aquatic organisms

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.

In a long term study, conducted with *Daphnia magna,* the most sensitive of the species tested in the short term studies the 21-day NOEC was determined to be 12.5 mg/L. Since short term studies from three trophic levels are available, and the long term study was conducted with

the most sensitive species, an assessment factor of 10 is used as recommended in TGD. The predicted no effect concentration for aquatic organisms ($PNEC_{water}$) is calculated to be 12.5/10 mg/L=1.25 mg/L.

Since piperazine is expected to be slowly degraded in the aquatic environment, this PNEC value based on long term effects will be used for the risk assessment also for the intermittent release scenarios. Also PNEC intermittent based on the lowest acute data and an assessment factor of 100, would be below the PNEC based on long term effect data and an assessment factor of 10. Taken together PNEC based on long term effects is considered to be the most justified value to be used for the intermittent release scenarios.

3.2.1.7 Predicted no effect concentration (PNEC) for sediment-dwelling organisms

Since no data are available for sediment-dwelling organisms, the $PNEC_{sediment}$ is estimated from $PNEC_{surface\ water}$ using the equilibrium partitioning equation as given in TGD. However, 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.

3.2.1.8 PNEC for micro-organisms in STP

According to TGD the $PNEC_{micro\text{-}organisms}$ is set equal to a NOEC from a test performed with specific bacterial populations like nitrifying bacteria and *Pseudomonas putida*. When this is applied on the results for *P. putida* presented above, a PNEC >1,000 mg/L is obtained. Using NOEC from the study with nitrifying bacteria results in PNEC < 74 mg/L (extrapolated value) it is however stated in TGD that results from the cell inhibition test with *P. putida* "should be treated with care" when used for effect assessment for STP.

Using results from other test systems, like the respiration inhibition test, the NOEC is divided with an assessment factor of 10. According to TGD, it should be noted that the effluent concentration is used for calculation of PEC/PNEC-quotients from these data, while heterotrophic micro-organisms in the aeration tank are probably exposed to a concentration more related to the influent concentration. Therefore a higher assessment factor is applied compared to the assessment factor for nitrifying bacteria. The $PNEC_{micro\text{-}organisms}$ based on the available respiration inhibition test is 540/10 = 54 mg/L. This value will be used in the further assessment of piperazine.

3.2.2 Atmosphere

3.2.2.1 Calculation of PNEC

No effect data for the atmospheric environment are available, and no $PNEC_{air}$ can be calculated.

3.2.3 Terrestrial compartment

3.2.3.1 Toxicity to terrestrial organisms

No standard studies are available on the toxicity of piperazine to terrestrial organisms.

3.2.3.2 Predicted no effect concentration (PNEC) for terrestrial organisms

Since no standard test data on terrestrial organisms are available, the $PNEC_{soil}$ is estimated from $PNEC_{water}$ using the equation:

$$PNECsoil = \frac{Ksoil - water}{RHOsoil} \cdot PNECwater \cdot 1000 \text{ (according to TGD page 339)}$$

Where $K_{soil\text{-}water}$ = 8.3 m^3/m^3 (derived from K_d 7.9 in soil sorption study)
RHO_{soil} = 1,700 kg/m^3
$PNEC_{water}$ = 1.25 mg/L (see Section 3.2.1.6)
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 (see Section 3.2.1.6).

3.2.4 Non compartment specific effects relevant to the food chain

No significant bioaccumulation or biomagnification is expected.

3.2.5 Summary of environmental effects

Table 3.12 Summary of available data on the environmental effects of piperazine

Species	Method	Results	Remark and reference
Micro-organisms *Pseudomonas putida*	ISO Guidelines, inhibition of cell multiplication.	18-hour NOEC>1,000 mg/L	Data on single species not suitable for PNEC calculation (van Ginkel, 1989)
Nitrifying bacteria	No guidelines.	2-hour EC_{10} 74 mg/L	Extrapolated value. Effects at all test concentrations (Balk and Meuwsen, 1989c)
Activated sludge	EEC Guidelines. Respiration inhibition, measurement of O_2-depletion.	0.5-hour NOEC 540 mg/L	This value was used for calculation of PNECstp (van Ginkel and Stroo, 1989)
Algae *Selenastrum capricornutum*	OECD 201	72-hour NOEC > 1,000 mg/L	(van Ginkel et al., 1990)
Crustaceans *Daphnia magna*	OECD 202: Static immobilisation test OECD 211: Daphnia reproduction	48-hour EC_{50} 21 mg/L 48-hour NOEC 10 mg/L 21-day NOEC 12.5 mg/L	(Balk and Meuwsen, 1989a) This value was used for calculation of PNECwater (Thomas et al., 2002)
Fish *Poecilia reticulata*	OECD 203: Semi-static test.	96-hour LC_{50} > 1,800 mg/L 96-hour NOEC 1,000 mg/L	(Balk and Meuwsen, 1989b)

The calculated predicted no effect concentrations in different environmental compartments that will be used in the risk assessment of piperazine are given in **Table 3.13**.

Table 3.13 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

3.3 RISK CHARACTERISATION

3.3.1 Aquatic compartment

Short-term effect studies on aquatic organisms, exposed to piperazine via water, are available for fish, aquatic invertebrates, algae and micro-organisms. A 21-day reproduction study is available for Daphnia. The NOEC from this study, 12.5 mg/L is used for the derivation of PNEC. Since the long term study was conducted with the most sensitive of the species tested in the short term studies, an assessment factor of 10 is used, as recommended in TGD. The predicted no effect concentration for aquatic organisms ($PNEC_{water}$) is calculated to 12.5/10 mg/L=1.25 mg/L.

No studies are available on effects to sediment dwelling organisms. Consequently, the $PNEC_{sediment}$ is calculated using the equilibrium partitioning method. Exposure levels and PEC/PNEC ratios for aquatic organisms and sediment dwellers at local point sources are given in the table below. Detailed assumptions for the exposure calculations for each local site are given in Appendix A-H (Annex C).

Table 3.14 Calculated local predicted environmental concentrations and PEC/PNEC ratios for surface water and sediment at known industrial point sources of piperazine. Bold figures for PEC/PNEC ratio indicate concern

Site	Life cycle stage	PEClocal, during emission (mg/L)		PEClocal (mg/kg ww)		PEC/PNEC Aquatic
		Surface water		Sediment		
		Site specific	Generic	Site specific	Generic	
A	Production	0.002*	0.008	0.002*	0.006	0.0014
B	Production	0.001*	1.3	0.001*	0.83	0.0005
C	Production	n.r.	1.5*	n.r.	1.2	1.2
D	Production / processing / formulation	0.20*	0.91	0.16*	0.71	0.16
E	Processing	0.001*	0.29	0.001*	0.23	0.0005
F	Processing / formulation	0.001*	2.6	0.001*	2.0	0.0005
G	Processing / formulation	0.002*	0.002	0.002*	0.002	0.0014
H	Formulation	n.r.	4.9*	n.r.	3.8*	3.9

n.r. No information submitted
* Figures based on site specific information.

Table 3.15 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

	PEClocal, during emission	PEClocal, annual mean	PEC/PNEC aquatic
	Ssurface water (mg/L)	Sediment (mg/kg ww)	
Industrial use of gas washers	0.02 - 29	0.01 - 23	0.02 - 23
Private use of pharmaceuticals	0.002	0.002	0.002

The PEC/PNEC ratios for aquatic organisms and sediment dwelling organisms were higher than 1 at 2 out of 8 known local industrial sites and at 21 out of 33 gas washer processing sites. Thus further site-specific information on exposure is required, such as specific emissions to surface waters and information on river flow and number of emission days. Some further information has been given; however even then assumptions had to be made (see Section 3.1.2.1.1). For private use of pharmaceuticals, at present no further information is needed. The data from the scenarios are further used for the calculation of exposure of man via the environment. For the gas-washer scenario, the most optimal information should be data on the releases of piperazine from all the sites.

Regional and continental PEC for the aquatic compartments were calculated by EUSES. The resulting exposure levels and PEC/PNEC ratios are given in **Table 3.16**.

Table 3.16 Regional and continental predicted environmental concentrations and PEC/PNEC ratios for surface water and sediment calculated based on generic scenarios by EUSES

Scenario	PEC surface water	PEC sediment	PEC/PNEC
Regional	0.59 μg/l	0.35 μg/kg ww	0.0005
Continental	0.04 μg/l	0.03 μg/kg ww	0.00004

The local PEC for STP sludge has been calculated according to TGD. The resulting exposure levels and PEC/PNEC ratios for micro-organisms in STP are given in the **Table 3.17** below.

Table 3.17 Calculated PEC/PNEClocal for microrganisms in STP for known industrial sites and for use patterns 6-8, for which there are no known specific local sites available. PNECmicroorganisms= 54mg/l.

Site	Life cycle stage / use pattern	PEClocal (mg/l)	PEC/PNEClocal
A	Production	0.12	0.002
B	Production	0.002	0.000037
C	Production	15	0.28
D	Production/processing/formulation	2.0	0.037
E	Processing	2.9	0.054
F	Processing/formulation	2.6	0.048
G	Processing/formulation	0.001	0.000019
H	Formulation	0.00005	0.00000093
Gas washer	6 processing	14.5 – 15,000	0.27 - 278
Pharmaceuticals	7 private use	0.007	0.00013

Thus, use pattern 6 industrial use of piperazine for gas washing gives a PEC/PNEC above 1 for a majority of the local sites.

Conclusions to the risk assessment for the aquatic compartment

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 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.

Exposure levels in the air at local production and processing sites are given in Section 3.1.3. Details on the calculations for each local site are given in Appendix A-I (Annex C).

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 $\mu g/m^3$. This value will be used in the assessment of human exposure via the environment.

Regional and continental PEC for the atmosphere were calculated by EUSES. The resulting exposure levels are given in Section 3.1.3.

Conclusions to the risk assessment for the atmosphere

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

3.3.3 Terrestrial compartment

Since no standard study is available on the toxicity of piperazine to soil dwelling organisms, the $PNEC_{soil}$ is calculated from $PNEC_{water}$ using the equilibrium partitioning method. 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 should need 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.

No direct release of piperazine is expected at the local point sources. Aerial deposition is considered to be insignificant, since the substance is rapidly photolysed in the atmosphere. Exposure via sludge application is also considered to be of little importance, since piperazine is assumed be directed to the aquatic phase to 100% (hardly soluble salts not taken into account).

However, the use of piperazine as anthelmintics for domestic animals may cause significant exposure to soil dwelling organisms. A worst-case scenario was constructed where chickens and piglets were treated with the highest recommended dose, using a model for veterinary products (Spaepen et al., 1997). Manure from indoor stocks of piglets and chickens are spread on arable land. The resulting local PEC_{soil} to be used for the risk characterisation for terrestrial ecosystems was 0.06 mg/kg ww or 0.12 mg/kg ww, respectively, for agricultural soil and grassland.

Besides soil organisms, dung fauna in faeces from treated animals that are kept outside can be expected to be exposed to high concentrations of piperazine. Several species of dung beetles that are of importance for the digestion of faeces are known to be under a threat of extermination (Wiktelius, 1996). However, there are too many uncertainties so no scenario can be constructed. In a later study with grazing for three years of cattle given both chemical and biological anthelmintics no environmental impact on soil nematodes was confirmed (Yeates et al., 2002).

Regional and continental PEC for the terrestrial environment were calculated by EUSES. The resulting exposure levels and PEC/PNEC ratios are given in **Table 3.18**.

Table 3.18 Regional and continental predicted environmental concentrations and PEC/PNEC ratios in agricultural soil calculated based on generic scenarios by EUSES. 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	0.00000004
Continental	0.000006	0.000000001
Local	120	0.02

Following the release of piperazine via manure to agricultural soil and grassland, leaching of the substance may lead to contamination of groundwater. The highest estimated local concentration in groundwater was calculated to 0.02 mg/L (see Section 3.1.4.1.1).

Regional and continental PEC for groundwater may be considered negligible, based on the EUSES calculations.

Conclusions to the risk assessment for the terrestrial compartment

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

3.3.4 Non compartment specific effects relevant to the food chain

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.

Conclusions to the risk assessment for secondary poisoning

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

4 HUMAN HEALTH

4.1 HUMAN HEALTH (TOXICITY)

4.1.1 Exposure assessment

4.1.1.1 General discussion

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 2.1**, Section 2.2.1.

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. Humans may be exposed via the oral route via food and drinking water. Based on information contained in Section 1 and 2 the following exposure routes for each exposed population are considered to be relevant for this assessment:

Occupational exposure:	via inhalation and via dermal routes
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
Via the environment:	via inhalation (air) and via oral routes (food and water)

Piperazine is a solid substance at room temperature (melting point 107°C). Piperazine as a substance is most often handled as solid flakes (white or translucent rhomboid, or flake-like crystals that are highly hygroscopic) or as a water solution (often 65%). The pH of a 65% solution is > 12, based on information that a 15 % solution has a pH of 12. However, the salts of piperazine are all slightly acidic in dilute solutions. The vapour pressure of solid piperazine is 39.2 Pa at 22.5°C. This value is used in the EASE model. The saturated vapour concentration at 22.5°C is calculated to be 1.4 g/m^3.

Increased temperature increases the volatilisation of piperazine. The vapour will condense at lower temperatures to form a mist (aerosol).

All situations of inhalation exposure to piperazine are a combination of exposure to piperazine as vapour, smaller and larger aerosol particles and particles with condensed piperazine on the surface. This might be a problem in the exposure assessment using models

(EASE) and when assessing measurements. The conversion factors used for calculating air concentrations are; 1 ppm = 3.58 mg/m^3; 1 mg/m^3 = 0.279 ppm.

The particle size in different environments may be important, either for local effects in the respiratory tract and for the absorption via the lung, or following clearance in the respiratory tract, exposure via the gastrointestinal tract. A mist may comprise very small particles with e.g. mass median diameter 0.1-0.3 μm. This kind of aerosol is generally generated at processes with higher temperatures, where the substance is volatilised and then condenses in the air. This is generally the case at the production and at most of the industrial uses of volatile chemicals. Piperazine as condensed vapour occurs always as the pure substance (the free base) and not as salt. The pure substance is highly alkalic and causes therefore more effect on the mucus membranes in the airways. No data on the particle size of airborne piperazine particles have been submitted.

One source of exposure to piperazine is the piperazine salts. The salts are considered to be solid matter with very low vapour pressure and the exposure is therefore to airborne solid aerosol and dermal exposure to solid particles. To estimate the importance of this source, there is a need to recalculate/transform the exposure to pure piperazine. The content of piperazine in some common used piperazine salts are shown in **Table 4.1**. These data are used for the calculation of the exposure to piperazine from figures of exposure to the salts.

Table 4.1 The content of piperazine in piperazine hexahydrate and in some piperazine salts

Piperazine salt	Piperazine content (%)
Adipate	37
Citrate	35
Dihydrochloride	50
Hexahydrate	44
Hydrochloride	48
Phosphate	42

4.1.1.2 Bioavailability

Based on toxicokinetic data and information on human exposure situations, bioavailability for different pathways of exposure have been derived (in %) and are used in the calculation of internal human exposure. The bioavailability of piperazine for humans is assumed to be 100% for all routes of exposure (inhalation, dermal and oral). However, it is acknowledged that the dermal absorption is likely to be overestimated by this figure.

4.1.1.3 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 are 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.

For all activities the exposure is strongly influenced by plant conditions and working procedures. Poor conditions of hygiene in a plant could lead to high background concentrations of piperazine. The presence of effective control measures can also have a great influence on the exposure.

Based on the physical-chemical information on piperazine (see Section 2.2.1) and descriptions of the manufacture and formulation/processing of products containing piperazine (see Section 2.2.1), 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.

Occupational exposure data were received from five sites (exposure by inhalation), including two producers, two users, and one site with both production and use. No measured data on dermal exposure during the production of piperazine flakes have been provided.

Measured exposure data from one production site are published (Hagmar et al., 1987). Exposure data from this site is reported to the Swedish Labour Inspectorate (GRACE Rexolin, 1988, 1989, 1990). Probably, the same methods for sampling and analysis were used at this production site in both these reports. In the Hagmar study, personal sampling was performed with all-glass, capillary-tip, 30-ml midget impingers containing HCl absorption solution. The sample was evaporated to dryness and redissolved in NaOH. A 0.5 µL aliquot was injected on a GC. More information on the method is found in Section 4.1.2.5.2 Studies in humans - "Allergic dermatitis". A problem with the sampling method is to sample both gaseous piperazine and airborne particles simultaneously. Uncertainties in the used sampling method in the studies have been discussed, with the notion that the method may underestimate the air concentrations. In common for all measured data is that no information on the distribution vapour/particles is submitted. Measurements from one site are said to include both vapour and particles (BASF, 1999). Data on the particle size distribution is not submitted in any of the exposure data. There is at present no validated method for sampling or analysis of airborne piperazine, although a new method is said to be under development.

Not all reported data include information on e.g. methods for sampling and chemical analysis used, the duration of measurements or task of workers, date when samples were collected or the type of sampling conducted (personal or area measurements).

No data on the realistic total number of exposed employees in the EU have been submitted by the industry, and no information on the sex and age of the exposed workers in the EU is available.

The following data were used for occupational exposure assessments for piperazine:

- physico-chemical data of piperazine and piperazine salts,
- physical state, vapour pressure at different temperatures, (see Section 1)
- qualitative and quantitative data regarding methods and use pattern of the product,
- temperature at which manufacture processes take place,
- amount of piperazine used in the different products (salts), and
- measured work place data from use of piperazine.

In this section on occupational exposure, inhalation and dermal exposure from the EASE-model (Estimation and Assessment of Substance Exposure) are presented. All models are made upon assumptions. The outputs are approximates. EASE is only intended to give generalised exposure data. The output from the EASE-model for piperazine can be found in Appendix 1. The exposure is assessed, by EASE, using the available information on the substance, process and work tasks. More detailed information on these parameters may lead to a more accurate exposure assessment. Because of;

- the limited number of measured data,
- the fact that the measured values may be underestimating the exposure (because of the methodological problems, see above),
- the limited information on how and under what circumstances the work is performed at the workplaces during the measurements, and
- the limited information on how much exposure in general may vary in-between different workplaces using piperazine.

the upper ranges of the EASE-estimations are used as reasonable worst case. In addition, the measured data give some support for this approach, because there are measured data that are close to the upper EASE estimates.

Piperazine base is an irritating and even corrosive agent, which means that exposure-limiting measures would be in use when handling the base. This is considered in the risk characterisation section.

The information on the use of personal protective equipment (PPE) at workplaces where exposure to piperazine may take place is limited.

Some information is provided from two producers (Scenario 1). At the production of aqueous solution and flakes, it is said, “high standards of skin care (gloves of neoprene) and personal hygiene are followed all times. Safety goggles must be used. Dust masks are available at the packaging at the production of flakes. Supplied-air respiratory equipment must be used during cleaning” (Delamine, 1998). Information from another producer says, "during the work the personal protective equipment worn encompasses protective goggles, protective footwear and protective gauntlets made of vinyl” (BASF, 1999).

No data on the use of PPE are given for uses of piperazine or piperazine salts in further chemical processes (i.e. Scenario 2 and 3).

Dermal exposure to piperazine salts in the work environments may occur directly to unprotected skin in handling of piperazine salts, and indirectly via contamination of the facilities.

The exposure to salts is assessed without taking account of the possible influence of personal protective equipment (PPE). Information of the effectiveness of PPE to reduce exposure to piperazine in practical situations is limited. The use of PPE normally reduces the level of exposure. PPE are usually intended for use during work operations entailing risk for increased exposure such as repair work, service and maintenance. The exposure may be reduced by PPE, but incorrect or careless use may lead to unforeseen and unexpected exposure. One example is when using protective gloves; the contaminated gloves may come in contact with the skin on e.g. the face. However, in the risk characterisation of the salts, the possible use of PPE has been discussed.

Some of the handling of piperazine may take place outdoors. At these situations, the weather situation e.g. the wind direction and velocity, atmospheric humidity, rain etc. influences the exposure. However, there was no information on when and where the handling is outdoors, and it has therefore not been considered further.

The database on occupational exposure of piperazine is very limited e.g. on the frequency, duration, contact, and control measures and the particle size of the piperazine. Because no information on the particle size distribution of piperazine has been provided, airborne dust is assumed mainly to be respirable.

In this risk assessment the occupational exposure during the different life cycle stages are summarised in three generic scenarios;

“Loading” covers all kind of work tasks at the places where the raw material (piperazine or piperazine salts) are handled and added to a process, like opening and emptying packaging, weighing etc. These work tasks, and by that the exposure, goes on for the whole day (8 hours) as a realistic worst case (RWC). Typically the duration of these work tasks are less than 8 hours.

“Final handling” covers all kind of work tasks at the places where the final product (piperazine or piperazine salts) are handled, like centrifugation, drying, weighing, filling of packaging etc. These work tasks, and by that the exposure, goes on for the whole day (8 hours) as a RWC. Like for “loading” the duration of these work tasks typically are less than 8 hours.

“Cleaning and maintenance” cover all kind of occasional work tasks like cleaning, service, repair and maintenance during periods of normal running of the process including stop in batch-wise processes. These work tasks, and by that the exposure, goes on for four hours per day as a RWC. However, for the gas-washer scenario the major cleaning and maintenance occurs for a few working days every 3-5 years during full stops of the processes. The RWC-value thus represents an 8 hour working day for this scenario.

The duration of the daily exposure at theses scenarios during typical circumstances are assumed to be shorter than 8 and 4 hours, respectively. The exposure time may also vary in between days. Ideally, there should also be technical or other measures undertaken at the

workplaces to reduce exposure, but this is not considered in the RWC estimate. Because of the irritating/corrosive/sensitising properties of piperazine, it is assumed that workers avoid direct exposure to some extent. Therefore, typical exposures are assumed to be 10% of the RWC for all scenarios and both for exposure via inhalation and dermal exposure. Although the 10%-value is arbitrarily set, it is perhaps corroborated by the measured data, which contains some values clearly less than the RWC-values.

At all scenarios higher exposure may occur during shorter periods during the work. This might be during work tasks closer to releases giving rise to inhalation exposure or dermal contact to contaminated details. Therefore a short-term exposure level (15 minutes) is assumed to be double the RWC-value for all scenarios.

4.1.1.3.1 Production of piperazine base, Scenario 1

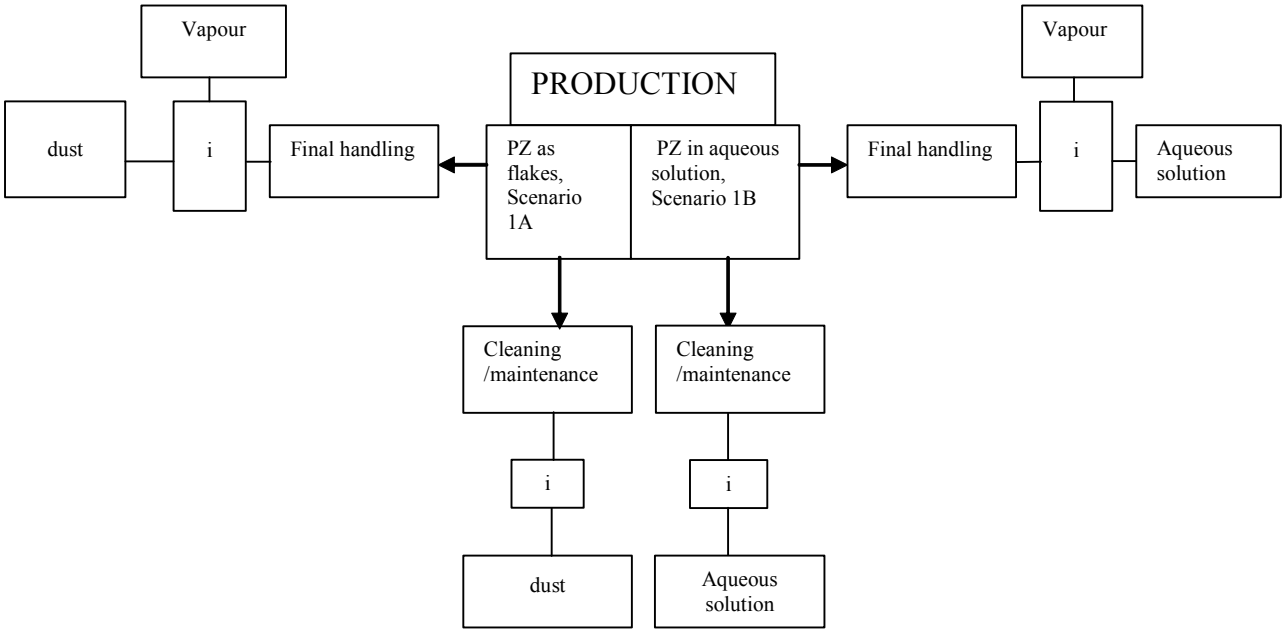
There are four sites with production of piperazine in the EU. The production process is described in Section 2.1.3

Today there are two production methods for piperazine used, i.e. the ethanolamine based process and the ethylene chloride based process. The production processes are closed and continuous for aqueous solutions, often placed out-doors in the open air, giving low levels of exposure. In contrast, the flake production is discontinuous. During packaging of flakes and cleaning of the equipment for flake production the processes are semi-closed. During flake production there can be local exhaust of dust.

Piperazine can be produced at one site and then be transported by trucks to the next site. During connection and disconnection there can be an emission of piperazine.

The production of piperazine takes place in closed systems. However, both inhalation and dermal exposure may occur, see Figure 4.1. Such exposure may occur during system leakage (breathing of a closed system), packaging, service and maintenance, transfer, process sampling, at incidental releases of piperazine, and during cleaning of e.g. the premises and of the tanks in which piperazine has been produced, stored or transported and other process equipment.

Figure 4.1 Exposure scenarios concerning production of piperazine base, Scenario 1A and 1B



i Exposure via inhalation

* Dermal exposure in these scenarios is assumed to be negligible as personal protective equipment (PPE) is assumed to be used because of the corrosive properties of the substance.

The production of flakes is more open than the production of water solutions. At the production of piperazine as flakes, piperazine can be spread as airborne dust. At production of aqueous solutions the release of piperazine to the air is as vaporisation and as aerosol. However the aerosol formation is assumed to be very limited.

Production of piperazine flakes, Scenario 1A

Measured data for exposure during production of piperazine flakes, Scenario 1A

Besides one published report (Hagmar and et al., 1987) containing exposure data but little information on working conditions, there is more detailed inhalation exposure data available from one site (**Table 4.2**). At this site, the equipment is "semi-closed": exposure is possible during packing the material in drums and during cleaning (once a day during 5 minutes). The process is a batch process (16 hours per day). Local exhaust (low pressure) is installed at the spot where dust can escape. At loading, dust mask are available. At cleaning, supplied-air respiratory equipment must be used. Production of flakes is going on 2 times 8 hours per day, 5 days per week and 45 weeks per year. 8 persons are involved in the flaking process during one week in a period of 4 weeks per person. The workers were exposed to both dust and vapour of piperazine.

Measurements have been carried out during different work tasks at two production sites. Exposure data for piperazine in production of piperazine flakes, Scenario 1A. **Table 4.2** is divided in the two units.

Table 4.2 Measured inhalation"cleaning/maintenance" and "final handling"

Cleaning and maintenance				
Year	Substance, activity	Concentration TWA mg/m^3 (sampling time)	Comment	Reference
May 1996-March 1998	Production of flakes, Cleaning	0.03-1.2 (Median 0.24)	19 samples. The cleaning takes place once a day during approximately 5 minutes	(Delamine, 1998)
Final handling				
Year	Substance, activity	Concentration TWA mg/m^3 (sampling time)	Comment	Reference
May 1996-July 1997	Production of flakes, Packaging (before improvement)	0.04 – 1.2 (Median 0.25)	14 samples	(Delamine, 1998)
July 1997-March 1998	Production of flakes, Packaging (after improvement –local exhaust)	0.02-0.08 (Median 0.04)	5 samples	(Delamine, 1998)
1980($5^{1.}$) 1981-83($4^{1.}$) 1984($3^{1.}$)	Flaking of piperazine hexahydrate (vapour)	0.26 ($10^{2.}$, 625 minutes) 0.42 ($10^{2.}$, 980 minutes) 0.11 ($11^{2.}$, 1246 minutes)	0.63 (17 minutes) 2.0 (113 minutes) 0.36 (150 minutes)	(Hagmar and et al., 1987)

1) Number of sampling periods
2) Number of samples

There is no measured data for dermal exposure during production of piperazine flakes, and since PPE is assumed to be used because of the corrosive properties of piperazine base, no dermal exposure is expected.

Model-generated data for exposure during production of piperazine flakes, Scenario 1A

Ranges for inhalation exposure determined with the EASE-model is given below.

Based on this model the estimates of exposure levels of piperazine are the following:

Inhalation exposure during cleaning and maintenance

Dust exposure to a non-fibrous solid is determined by: the process operations (Dry manipulation), whether the solid aggregates readily (No) and the pattern of control (LEV absent), resulting in an exposure range of 5-50 mg/m^3. During cleaning and maintenance, it may be assumed that the equipment is rinsed with a suitable solvent or vacuum cleaned, leaving a portion (say 10%) of the original concentration, resulting in an exposure range of 0.5-5 mg/m^3. This is considered to be an infrequent exposure situation (4 hours/day), even though industry reports the cleaning period as 5 minutes per day. The output from the EASE-model for piperazine is in Appendix 1 (EASE 4).

Inhalation exposure during final handling

Inhalation exposure to the gas, vapour or liquid aerosol of piperazine at a process temperature of 20°C is determined by: the pattern of use (Non-dispersive use), the pattern of control (LEV) and the ability of the substance to become airborne (low) resulting in an exposure range of 0.5-1.0 ppm (1.8-3.6 mg/m^3).

Dust exposure to a non-fibrous solid is determined by: the process operations (Dry manipulation), whether the solid aggregates readily (No) and the pattern of control (LEV present), resulting in an exposure range of 2-5 mg/m^3.

The output from the EASE-model for piperazine is in Appendix 1 (EASE 1, EASE 2).

The total exposure via inhalation (vapour and dust) can be calculated resulting in an exposure range of 3.6-8.6 mg/m^3.

Ranges for dermal exposure determined with the EASE-model is given below.

Dermal exposure during cleaning/maintenance;

Dermal exposure in this scenario is assumed to be negligible as personal protective equipment (PPE) is assumed to be used because of the corrosive properties of the substance.

Dermal exposure during final handling

Dermal exposure in this scenario is assumed to be negligible as personal protective equipment (PPE) is assumed to be used because of the corrosive properties of the substance.

Production of piperazine in aqueous solution, Scenario 1B

Methods for the production of piperazine are described in Section 2.1.3.

Measured data for exposure during production of piperazine aqueous solution, Scenario 1B

Measurements of inhalation exposure have been carried out during different work tasks at one production site producing piperazine in aqueous solution (**Table 4.3**). The duration of the exposure measurements were limited to the time in which piperazine was handled. No measurements of exposure were carried out during this normal operation of the production. The piperazine formed is separated via a pipe.

Depending on the production volume, cleaning is carried out once a day or once a month, monthly cleaning being most common. This step lasts for approximately half an hour. In addition, once or twice per shift there is an inspection round of the unit by a member of staff, which lasts for about five minutes. On account of the short duration of this task no exposure could be established.

The piperazine delivered in heatable tank trucks is heated up to about 75ºC for purposes of unloading. Measurements were carried out during connection and disconnection of the tank trucks including sampling from the dome of the tanks. Approximately 50 tank trucks deliveries are made per annum.

In the loading unit one member of staff is employed per shift and exposure is possible. The workflow involves several steps, and the total time working directly at the unit is approximately 1 hour per shift=1/8 of a shift.

During the work the personal protective equipment worn encompasses protective goggles, protective footwear and protective gauntlets made of vinyl.

Table 4.3 Measured inhalation exposure data for production of piperazine in aqueous solution, during final handling, Scenario1B

Year	Substance, activity	Concentration TWA mg/m3 (sampling time)	Comment	Reference
1999	Tank truck connection	<0.071	65% piperazine delivered in heatable tanks (75C)	(BASF AG, July 1999)
1999	Tank truck disconnection	0.11	"	
1999	Tank truck connection/including sampling	4.4	"	
1999	Tank truck disconnection	0.17	"	
1999	Filling units/Scales	0.17	Filling of boxes, stationary sampling	
1999	Directly at filling nozzle	0.13	"	
1999	"	0.33	"	
1999	"	0.14	"	
1999	Drying belt/Inspection window	1.3	"	
1999	Drying belt /Centre	1.5	"	

Cleaning and maintenance

No measured data for cleaning and maintenance is provided for production of piperazine aqueous solution.

Final handling

Measured exposure data for production of piperazine in water solution, shown in **Table 4.3**, may be considered as final handling.

There is no measured data for dermal exposure during production of piperazine flakes

Model-generated data for exposure during production of piperazine aqueous solution (Scenario 1B)

Inhalation exposure during cleaning and maintenance

Inhalation exposure to the gas, vapour or liquid aerosol of piperazine at a process temperature of 20 is determined by: the pattern of use (Non-dispersive use), the ability of the substance to become airborne (low) and the level of control applied to the handling (direct handling with dilution ventilation) resulting in an exposure range 10-20 ppm (35.8-71.6 mg/m^3). During cleaning and maintenance, it may be assumed that the equipment is rinsed with a suitable solvent or vacuum cleaned, leaving a portion (say 10%) of the original concentration, resulting in an exposure range of 3.6-7.2 mg/m^3. This is considered to be an infrequent exposure situation (4 hours/day), although industry information indicates cleaning half an hour once a day to once a month. The output from the EASE-model for piperazine is in Appendix 1 (EASE 6).

Inhalation exposure during final handling

Inhalation exposure to the gas, vapour or liquid aerosol of piperazine at a process temperature of 20 is determined by: the pattern of use (Non-dispersive use), the pattern of control (LEV) and the ability of the substance to become airborne (low) resulting in an exposure range of 0.5-1.0 ppm (1.8-3.6 mg/m^3)

The output from the EASE-model for piperazine is in Appendix 1 (EASE 1).

Ranges for dermal exposure determined with the EASE-model are given below.

Dermal exposure during cleaning and maintenance

Dermal exposure in this scenario is assumed to be negligible as personal protective equipment (PPE) is assumed to be used because of the corrosive properties of the substance.

Dermal exposure during final handling

Dermal exposure in this scenario is assumed to be negligible as personal protective equipment (PPE) is assumed to be used because of the corrosive properties of the substance.

4.1.1.3.2 Conclusion: Scenario 1. Production of piperazine base.

The product is piperazine flakes or piperazine in aqueous solution. The highest exposure to piperazine via inhalation, at the manufacture site is assumed to be during the "final handling" and during "cleaning and maintenance". Dermal exposure at the production of piperazine is assumed to be negligible as personal protective equipment (PPE) is assumed to be used because of the corrosive properties of the substance. The other manufacturing steps are assumed to be closed and the release of piperazine to the working environment is probably low during normal conditions.

Production of flakes

Considering all available data for exposure during production of piperazine flakes, a RWC for exposure via inhalation during "final handling" is assumed to be 3.6 mg/m^3 (vapour), and 5.0 mg/m^3 (dust) (8-hour TWA), giving a total of 8.6 mg/m^3. Typical exposure during production of piperazine flakes is assumed to be 10% of the RWC. Short term exposure for 15 minutes is assumed to be 200% of the RWC.

During cleaning and maintenance, exposure via inhalation is estimated to be 5.0 mg/ m^3 (dust) (4-hour TWA), which is probably overestimating the exposure considering the reported cleaning periods. The latter value is not used in the risk characterisation.

Production of aqueous solution

Considering all available data for exposure during production of piperazine in aqueous solution, a RWC for exposure via inhalation during "final handling" is assumed to be 3.6 mg/m^3 (vapour) (8-hour TWA).

Typical exposure during production of piperazine flakes is assumed to be 10% of the RWC. Short-term exposure for 15 minutes is assumed to be 200% of the RWC.

During cleaning and maintenance, exposure via inhalation is estimated to be 72 mg/m^3 (vapour) (4-hour TWA), which is probably overestimating the exposure considering the reported cleaning periods. The latter value is not used in the risk characterisation.

4.1.1.3.3 Industrial use of piperazine base, Scenario 2

Different industrial uses of piperazine are described more in detail in Section 2.2.

Industrial uses of piperazine are following:

- production of piperazine salts, 2A, from piperazine flakes (2A flakes) or from aqueous piperazine (2A aqueous)
- synthesis of other substances, 2B, from piperazine flakes (2B flakes) or from aqueous piperazine (2B aqueous)
- formulation with piperazine salts, 2C

Piperazine base is used in the manufacture of polycondensation resins and polymers (co-polyamides, polyurethanes), corrosion inhibitors; hardeners for epoxy resins, phenothiazine, drugs, etc.

Several piperazine products are used for manufacture of veterinary medicines for intestinal parasites. In non-EU countries (and earlier in EU), similar medicines are made for human use. Piperazine is also used as a basis for a large number of medicines, for accelerators in the rubber industry, in antioxidants, corrosion inhibitors, surfactants, fibres, resins, insecticides and textile dyes, and also within analytical chemistry.

Patents of uses of piperazine for gas-washing applications have been published (see Section 2.2.3). Exposure to piperazine may occur in vapour form and in some cases as dust. Exposure to salts is solely in the form of dust.

No data on the number of sites using piperazine or piperazine salts have been submitted (see Annex C).

Workers in the industry using piperazine are potentially exposed, especially those workers who are working directly in contact with the substance. Activities leading to direct contact concerns workers handling the pure piperazine, the different piperazine salts or products containing piperazine and workers transferring the substance or products to other systems in the chemical industries. Workers involved in the adding of the substance are potentially exposed. Exposure may occur when adding (charging) piperazine in the processes, during mixing the agent, during sampling, during service and maintenance, during cleaning the rooms and at system leaks.

Manual charging of piperazine to the process is assumed to be the working task during normal operation of processes with the highest exposure. In this assessment the exposure when adding piperazine is assumed to be the same at all processes irrespective of the kind of processes.

The handling of piperazine at formulation/processing may be more open processes than during production. This includes all kind of processes where the substance is added to a process including e.g. synthesis processes and gas washer processes.

Exposure may occur in the following situations during the manufacture of piperazine salts, polycondensation resins and polymers (copolyamides, polyurethanes), corrosion inhibitors, hardeners for epoxy resins, phenothiazine, drugs, etc.

According to data from the U.K. Health and Safety Executive (HSE), the U.K. industry explains that the most likely activities where exposure may occur during the use of piperazine are:

- Weighing and mixing small amounts of piperazine with other additives and adding the dry mix to a mixer vessel at 20°C; and,
- Emptying large amounts of piperazine from full kegs into a reactor vessel at 60°C.

The first task will be undertaken typically once every three month and takes about fifteen minutes. During the second task, the kegs of piperazine will be opened manually in the area immediately adjacent to the reactor at 20°C and then emptied into the reactor, which is maintained typically at about 60°C.

The EASE predictions for personal exposures to workers employed in these activities are summarised in **Table 4.4**. EASE predicts that 8-hour TWA exposures can be controlled to less than 8.9 mg/m^3 whilst short-term exposures will lie in the range of 3.8 to 76.6 mg/m^3.

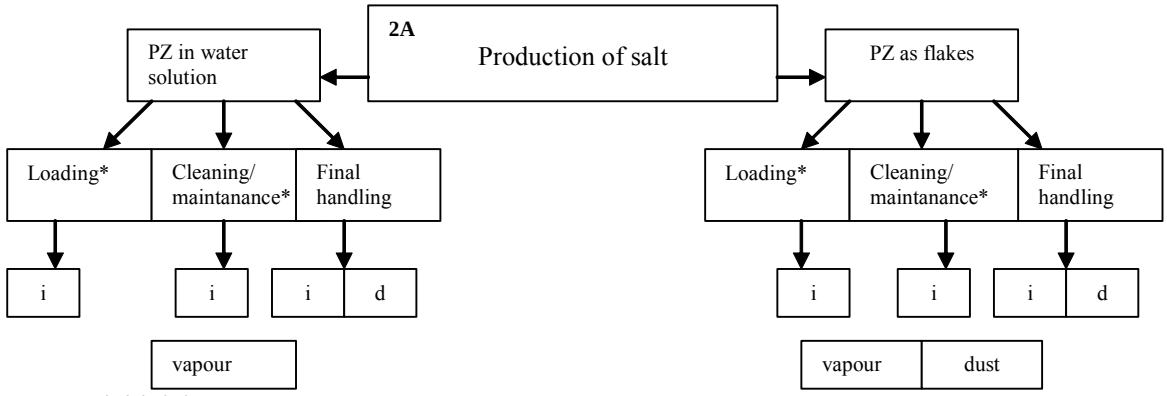
Table 4.4 Worker exposure to piperazine according to UK Watch documentation

Process	8-hour TWA (mg/m^3)	Short-Term (mg/m^3)
Weighing, mixing and blending of small amounts of piperazine at 20°C	0.1-0.3	3.8-8.6
Charging reactor with large amounts of piperazine at 60°C	4.7-8.9	37.8-76.6

Production of piperazine salt from piperazine flakes or piperazine aqueous solution, Scenario 2A (divided into two sub-scenarios for flakes and aqueous solution, respectively)

The exposures at Scenario 2A, production of piperazine salt from piperazine flakes or aqueous solution is described in **Figure 4.2**.

Figure 4.2 Exposure scenarios concerning production of piperazine salts.



i exposure via inhalation
d dermal exposure

* dermal exposure in these scenarios is assumed to be negligible as personal protective equipment (PPE) is assumed to be used because of the corrosive properties of the substance.

Scenario 2A, piperazine flakes

Measured inhalation exposure data is presented in **Table 4.5**.

Table 4.5 Measured exposure data for piperazine in industrial use; Scenario 2A, production of piperazine salts from flakes. The table is divided in three parts: Loading, cleaning/maintenance and final handling

Loading				
Year	Substance, activity	Concentration TWA mg/m^3 (sampling time)	Comment	Reference
1988	Intake from piperazine container and sampling TWAs	0.02 0.09 0.71	Stationary (0.36-0.56)	(GRACE Rexolin, 1988, 1989, 1990)
1980(9[1.]) 1981-83(5[1.]) 1984 (8[1.])	Flaking of anhydrous. piperazine (vapour)	1.2 (32[2.], 2,255 minutes) 0.73 (15[2.], 1,239 minutes) 0.63 (39[2.], 4,800 minutes)	100 (0.5 minutes) 6.4 (93 minutes) 9.2 (2.3 minutes)	(Hagmar and et al., 1987)
1980(5*) 1981-83(4[1.]) 1984(3[1.])	Flaking of piperazine hexahydrate (vapour)	0.26 (10[2.], 625 minutes) 0.42 (10[2.], 980 minutes) 0.11 (11[2.], 1246 minutes)	0.63 (17 minutes) 2.0 (113 minutes) 0.36 (150 minutes)	(Hagmar and et al., 1987)
Cleaning/ Maintenance				
Year	Substance, activity	Concentration TWA mg/m^3 (sampling time)	Comment	Reference
1988	Cleaning of vessels for piperazine	0.24 (228 minutes, stationary)		(GRACE Rexolin, 1988, 1989, 1990)
Final handling				
Year	Substance activity	Concentration TWA mg/m^3 (sampling time)	Comment	Reference
1988, -89, -91	Piperazine adipate	<0.01-0.11		(GRACE Rexolin, 1988, 1989, 1990)
1989, -90, -91	Piperazine citrate (manufacturing)	<0.01-0.05 0.03-0.09 (stationary)		
1989, -90, -91	Piperazine dihydrochloride (manufacturing)	<0.01-0.6	Disturbance in the process Stationary sampl. 0.02-0.13	
1989, -90, -91	Piperazine hexahydrate	0.01-1.04		
1989, -91	N-methyl piperazine	0.1-1.3 (NMP) 0.1-2.4 (NMP, stationary) 0.6-1.4 (DMP) 0.7-2.3 (DMP, stationary)	Filling of barrels	

Table 4.5 continued overleaf

Table 4.5 continued Measured exposure data for piperazine in industrial use; Scenario 2A, production of piperazine salts from flakes. The table is divided in three parts: Loading, cleaning/maintenance and final handling

Final handling				
Year	Substance activity	Concentration TWA mg/m3 (sampling time)	Comment	Reference
1989, -90, -91	N-methyl piperazine	0.01-0.04 0.03-0.06 (N-methyl piperazine) 0.01-0.04 (N,N dimethyl piperazine)		(GRACE Rexolin, 1988, 1989, 1990)
1990	Di-methyl piperazine, DMP	0.1-0.4 (personal sampl) 0.1-0.5 (stationary)		
1989,	Piperazine monophosphate	<0.01-0.36		
1980-85(6[1.])	Centrifugation of piperazine salts (dust)	0.06 (25[2.], 2,960 minutes)	0.80 (67 minutes)	(Hagmar and et al., 1987)
1982-84(12[1.]) 1985(6[1.])	Granulation of piperazine salts (dust)	0.09 (22[2.], 3,128 minutes) 0.08 (30[2.], 2,389 minutes)	0.42 (70 minutes) 7.4 (9 minutes)	

1) Number of sampling periods
2) Number of samples

No data on dermal exposure during production of piperazine salts from piperazine flakes has been submitted.

EASE-Model generated data for exposure during production of piperazine salts from piperazine flakes, Scenario 2A**,** are given in **Table 4.6**.

Inhalation exposure during loading

Inhalation exposure to the gas, vapour or liquid aerosol of piperazine at a process temperature of 20 is determined by: the pattern of use (Non-dispersive use), the pattern of control (LEV) and the ability of the substance to become airborne (low) resulting in an exposure range of 0.5-1.0 ppm (1.8-3.6 mg/m^3).

Dust exposure to a non-fibrous solid is determined by: the process operations (Dry manipulation), whether the solid aggregates readily (No) and the pattern of control (LEV present), resulting in an exposure range of 2-5 mg/m3

The total exposure via inhalation (vapour and dust) can be calculated resulting in an exposure range of 3.6-8.6 mg/m^3.

The output from the EASE-model for piperazine is in Appendix 1 (EASE 1, EASE 2).

Inhalation exposure during cleaning/maintenance

Dust exposure to a non-fibrous solid is determined by: the process operations (Dry manipulation), whether the solid aggregates readily (No) and the pattern of control (LEV absent), resulting in an exposure range of 5-50 mg/m3. During cleaning and maintenance, it may be assumed that the equipment is rinsed with a suitable solvent or vacuum cleaned, leaving a portion (say 10%) of the original concentration, resulting in an exposure range of 0.5-5 mg/m^3. This is considered to be an infrequent exposure situation (4 hours/day).

The output from the EASE-model for piperazine is in Appendix 1 (EASE 4).

Inhalation exposure during final handling

Dust exposure to a non-fibrous solid is determined by: the process operations (Dry manipulation), whether the solid aggregates readily (No) and the pattern of control (LEV present), resulting in an exposure range of 2-5 mg/m^3

The output from the EASE-model for piperazine is in Appendix 1 (EASE 2).

The exposure to piperazine during the exposure to airborne salt can be calculated by multiplying the salt concentration with the fraction of piperazine in the salt. The modelled exposures to piperazine salts by EASE are listed in **Table 4.6**.

Table 4.6 Piperazine exposure by inhalation (mg/m^3) at the production of piperazine salts from piperazine flakes, generated by EASE. The exposures of piperazine are calculated from the exposure to the salt dust (generated by EASE) and the fraction of piperazine in each salt

Piperazine salt	Piperazine exposure in mg/m^3 during final handling, (assuming a conc. of 2-5 mg/m^3 dust) 8-hour TWA	Piperazine exposure in mg/m^3 during cleaning/maintenance [assuming a conc. of 0.5 – 5 mg/m^3 dust (salt)] 4-hour exposure
Adipate (37%)	0.7-1.9	0.2-1.9
Citrate (35%)	0.7-1.8	0.2-1.8
Dihydrochloride (50-53%)	1.0-2.5	0.3-2.5
Hexahydrate (44%)	0.9-2.2	0.2-2.2
Hydrochloride (48%)	1-2.4	0.2-2.4
Phosphate (42%)	0.8-2.1	0.2-2.1

Ranges for dermal exposure determined with the EASE-model are given in **Table 4.7**.

Dermal exposure during loading

Dermal exposure in this scenario is assumed to be negligible as personal protective equipment (PPE) is assumed to be used because of the corrosive properties of the substance.

Dermal exposure during cleaning and maintenance

Dermal exposure in this scenario is assumed to be negligible as personal protective equipment (PPE) is assumed to be used because of the corrosive properties of the substance.

Dermal exposure during final handling

Dermal exposure to a substance, which is directly handled, is determined by the use pattern (Non-dispersive use) and the contact level (Intermittent), resulting in an exposure range of 0.1-1 mg/cm^2/day.

The output from the EASE-model for piperazine is in Appendix 1 (EASE 3).

The exposure to piperazine during the exposure to airborne salt can be calculated by multiplying the salt concentration with the fraction of piperazine in the salt. The modelled exposures to piperazine salts by EASE are listed in **Table 4.7**.

Table 4.7 Piperazine dermal (mg/m²/day) at the production of piperazine salts generated by EASE. The exposures of piperazine are calculated from the exposure to the salt dust (generated by EASE) and the fraction of piperazine in each salt

Piperazine salt	Piperazine dermal exposure in mg/m³ during final handling, (assuming an exposure of 0.1-1 mg/cm²/day) 8-hour TWA
Adipate (37%)	0.04-0.4
Citrate (35%)	0.04-0.4
Dihydrochloride (50-53%)	0.05-0.5
Hexahydrate (44%)	0.04-0.4
Hydrochloride (48%)	0.05-0.5
Phosphate (42%)	0.04-0.4

Scenario 2A, aqueous piperazine solution

Measured data for exposure during production of piperazine salts from piperazine aqueous solution

No measured data exposure during the production of piperazine salts from piperazine aqueous solution has been provided.

Modelled data for exposure during production of piperazine salts from piperazine aqueous solution

Ranges for inhalation exposure determined with the EASE-model are given in **Table 4.8**

Inhalation exposure during loading

Inhalation exposure to the gas, vapour or liquid aerosol of piperazine at a process temperature of 20 is determined by: the pattern of use (Non-dispersive use), the pattern of control (LEV) and the ability of the substance to become airborne (low) resulting in an exposure range of 0.5-1.0 ppm (1.8-3.6 mg/m^3)

The output from the EASE-model for piperazine is in Appendix 1 (EASE 1).

Inhalation exposure during cleaning and maintenance

Inhalation exposure to the gas, vapour or liquid aerosol of piperazine at a process temperature of 20 is determined by: the pattern of use (Non-dispersive use), the ability of the substance to become airborne (low) and the level of control applied to the handling (Direct handling with dilution ventilation) resulting in an exposure range 10-20 ppm (35.8-71.6 mg/m^3). During cleaning and maintenance, it may be assumed that the equipment is rinsed with a suitable solvent or vacuum cleaned, leaving a portion (say 10%) of the original concentration, resulting in an exposure range of 3.6-7.2 mg/m^3. This is considered to be an infrequent exposure situation (4 hours/day).

The output from the EASE-model for piperazine is in Appendix 1 (EASE 6).

Inhalation exposure during final handling

Dust exposure to a non-fibrous solid is determined by: the process operations (Dry manipulation), whether the solid aggregates readily (No) and the pattern of control (LEV present), resulting in an exposure range of 2-5 mg/m^3 piperazine salt.

The output from the EASE-model for piperazine is in Appendix 1 (EASE 2).

The exposure to piperazine during the exposure to airborne salt can be calculated by multiplying the salt concentration with the fraction of piperazine in the salt. The modelled exposures to piperazine salts by EASE are listed in **Table 4.8**.

Table 4.8 Piperazine exposure by inhalation (mg/m^3) at the production of piperazine salts generated by EASE. The exposures of piperazine are calculated from the exposure to the salt dust (generated by EASE) and the fraction of piperazine in each salt.

Piperazine salt (% piperazine content in the salt)	Piperazine exposure in mg/m^3 during final handling, (assuming a conc. of 2-5 mg/m^3 dust) 8-hour TWA	Piperazine exposure in mg/m^3 during cleaning/maintenance [assuming a conc. of 3.6-7.2 mg/m^3 dust (salt)] 4-hour exposure
Adipate (37%)	0.7-1.9	0.13-2.7
Citrate (35%)	0.7-1.8	0.13-2.5
Dihydrochloride (50-53%)	1.0-2.5	1.9-3.8
Hexahydrate (44%)	0.9-2.2	1.6-3.2
Hydrochloride (48%)	1-2.4	1.7-3.4
Phosphate (42%)	0.8-2.1	1.5-3.0

Ranges for dermal exposure determined with the EASE-model are given in **Table 4.9**

Dermal exposure during loading

Dermal exposure in this scenario is assumed to be negligible as personal protective equipment (PPE) is assumed to be used because of the corrosive properties of the substance.

Dermal exposure during cleaning and maintenance

Dermal exposure in this scenario is assumed to be negligible as personal protective equipment (PPE) is assumed to be used because of the corrosive properties of the substance.

Dermal exposure during final handling

Dermal exposure to a substance, which is directly handled, is determined by the use pattern (Non-dispersive use) and the contact level (Intermittent), resulting in an exposure range of 0.1-1 mg/cm^2/day. The output from the EASE-model for piperazine is in Appendix 1 (EASE 3).

The exposure to piperazine during the exposure to airborne salt can be calculated by multiplying the salt concentration with the fraction of piperazine in the salt. The modelled exposures to piperazine salts by EASE are listed in **Table 4.9**.

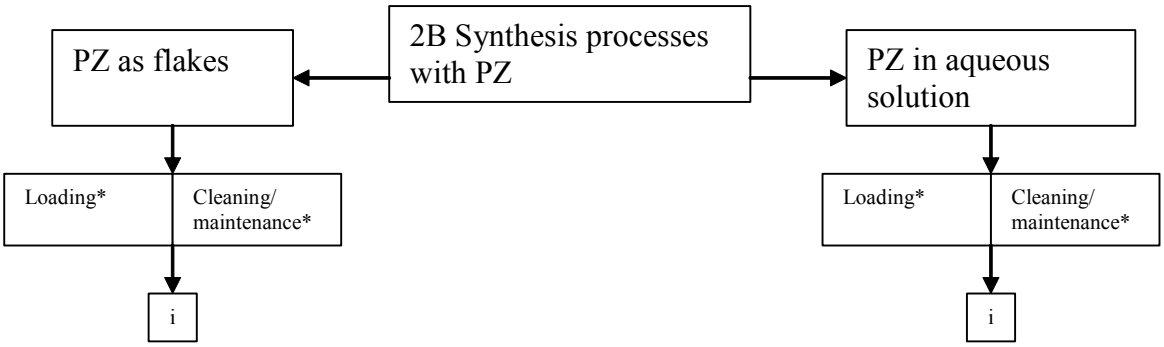
Table 4.9 Piperazine dermal exposure (mg/cm²/day) at the production of piperazine salts generated by EASE. The exposures of piperazine are calculated from the exposure to the salt dust (generated by EASE) and the fraction of piperazine in each salt

Piperazine salt	Piperazine dermal exposure during final handling, (assuming an exposure of 0.1-1 mg/cm²/day)
Adipate (37%)	0.04-0.4
Citrate (35%)	0.04-0.4
Dihydrochloride (50-53%)	0.05-0.5
Hexahydrate (44%)	0.04-0.4
Hydrochloride (48%)	0.05-0.5
Phosphate (42%)	0.04-0.4

The highest exposure to piperazine at the manufacture of piperazine salts is assumed to be during the packaging and cleaning. The other process steps at the production of piperazine salts are assumed to be closed and the release to the working environment is probably low during normal conditions.

Synthesis processes with piperazine flakes or aqueous solution, Scenario 2B
(divided into two sub-scenarios for flakes and aqueous solution, respectively)

Figure 4.3 Exposure scenarios concerning synthesis processes with piperazine



i exposure via inhalation
* dermal exposure in these scenarios is assumed to be negligible as personal protective equipment (PPE) is assumed to be used because of the corrosive properties of the substance.

Scenario 2B piperazine flakes

Measured data for exposure during synthesis processes with piperazine flakes, Scenario 2B

No data on exposure during synthesis processes with piperazine flakes have been submitted.

Modelled data for exposure during synthesis processes with piperazine flakes, Scenario 2B

Inhalation exposure during loading

Inhalation exposure to the gas, vapour or liquid aerosol of piperazine at a process temperature of 20 is determined by: the pattern of use (Non-dispersive use), the pattern of control (LEV) and the ability of the substance to become airborne (low) resulting in an exposure range of 0.5-1.0 ppm (1.8-3.6 mg/m^3).

The output from the EASE-model for piperazine is in Appendix 1 (EASE 1).

Dust exposure to a non-fibrous solid is determined by: the process operations (Dry manipulation), whether the solid aggregates readily (No) and the pattern of control (LEV present), resulting in an exposure range of 2-5 mg/m^3

The output from the EASE-model for piperazine is in Appendix 1 (EASE 2).

The total exposure via inhalation is 3.6-8.6 mg/m^3.

Inhalation exposure during cleaning and maintenance

Dust exposure to a non-fibrous solid is determined by: the process operations (Dry manipulation), whether the solid aggregates readily (No) and the pattern of control (LEV absent), resulting in an exposure range of 5-50 mg/m^3.

During cleaning and maintenance, it may be assumed that the equipment is rinsed with the suitable solvent or vacuum cleaned, leaving a portion (say 10% of the original concentration, resulting in an exposure range of 0.5-5 mg/m^3. This is considered to be an infrequent exposure situation (4 hours/day).

The output from the EASE-model for piperazine is in Appendix 1 (EASE 4).

Dermal exposure during loading

Dermal exposure in this scenario is assumed to be negligible as personal protective equipment (PPE) is assumed to be used because of the corrosive properties of the substance.

Dermal exposure during cleaning and maintenance

Dermal exposure in this scenario is assumed to be negligible as personal protective equipment (PPE) is assumed to be used because of the corrosive properties of the substance.

Scenario 2B, aqueous piperazine solution

Measured data for exposure during synthesis processes with piperazine in aqueous solution, Scenario 2B

No exposure data on exposure during synthesis processes with piperazine in aqueous solution has been submitted.

Modelled data for exposure during synthesis processes with piperazine aqueous solution, Scenario 2B

Inhalation exposure during loading

Inhalation exposure to the gas, vapour or liquid aerosol of piperazine at a process temperature of 20 is determined by: the pattern of use (Non-dispersive use), the pattern of control (LEV) and the ability of the substance to become airborne (low) resulting in an exposure range of 0.5-1.0 ppm (1.8-3.6 mg/m^3).

The output from the EASE-model for piperazine is in Appendix 1 (EASE 1).

Inhalation exposure during cleaning and maintenance

Inhalation exposure to the gas, vapour or liquid aerosol of piperazine at a process temperature of 20 is determined by: the pattern of use (Non-dispersive use), the ability of the substance to become airborne (low) and the level of control applied to the handling (Uncontrolled direct handling) resulting in an exposure range 10-20 ppm (35.8-71.6 mg/m^3). During cleaning and maintenance, it may be assumed that the equipment is rinsed with a suitable solvent or vacuum cleaned, leaving a portion (say 10%) of the original concentration, resulting in an exposure range of. 3.6-7.2 mg/m^3. This is considered to be an infrequent exposure situation (4 hours/day).

The output from the EASE-model for piperazine is in Appendix 1 (EASE 6).

Dermal exposure during loading

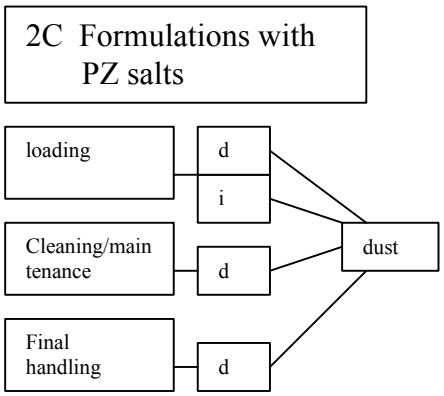
Dermal exposure in this scenario is assumed to be negligible as personal protective equipment (PPE) is assumed to be used because of the corrosive properties of the substance.

Dermal exposure during cleaning and maintenance

Dermal exposure in this scenario is assumed to be negligible as personal protective equipment (PPE) is assumed to be used because of the corrosive properties of the substance.

Formulations with piperazine salts, Scenario 2C

Figure 4.4 Exposure scenarios concerning formulation with piperazine salts.



i exposure via inhalation
d dermal exposure

Measured data for exposure during formulations with piperazine salts, Scenario 2C

No measured data for exposure during formulations with piperazine salts has been submitted.

Modelled data for exposure during formulations with piperazine salts, Scenario 2C

Inhalation exposure during loading:

Dust exposure to a non-fibrous solid is determined by: the process operations (Dry manipulation), whether the solid aggregates readily (No) and the pattern of control (LEV present), resulting in an exposure range of 2-5 mg/m^3.

The output from the EASE-model for piperazine is in Appendix 1 (EASE 2).

Inhalation exposure during cleaning and maintenance

Dust exposure to a non-fibrous solid is determined by: the process operations (Dry manipulation), whether the solid aggregates readily (No) and the pattern of control (LEV absent), resulting in an exposure range of 5-50 mg/m^3. During cleaning and maintenance, it may be assumed that the equipment is rinsed with a suitable solvent or vacuum cleaned, leaving a portion (say 10%) of the original concentration, resulting in an exposure range of 0.5-5 mg/m^3. This is considered to be an infrequent exposure situation (4 hours/day).

The output from the EASE-model for piperazine is in Appendix 1 (EASE 4).

The exposure to piperazine during the exposure to airborne salt can be calculated by multiplying the salt concentration with the fraction of piperazine in the salt. The modelled exposures to piperazine salts by EASE are listed in **Table 4.10**.

Table 4.10 Piperazine exposure by inhalation (mg/m^3) at the production of piperazine salts generated by EASE. The exposures of piperazine are calculated from the exposure to the salt dust (generated by EASE) and the fraction of piperazine in each salt.

Piperazine salt	Piperazine exposure in mg/m^3 during final handling, (assuming a conc. of 2-5 mg/m^3 dust) 8-hour TWA	Piperazine exposure in mg/m^3 during cleaning/maintenance [assuming a conc. of 0.5-5 mg/m^3 dust (salt)] 4-hour exposure
Adipate (37%)	0.7-1.9	0.2-1.9
Citrate (35%)	0.7-1.8	0.2-1.8
Dihydrochloride (50-53%)	1.0-2.5	0.3-2.5
Hexahydrate (44%)	0.9-2.2	0.2-2.2
Hydrochloride (48%)	1-2.4	0.2-2.4
Phosphate (42%)	0.8-2.1	0.2-2.1

Dermal exposure during loading

Dermal exposure to a substance, which is directly handled, is determined by the use pattern (Non-dispersive use) and the contact level (Intermittent), resulting in an exposure range of 0.1-1 mg/cm^2/day

The output from the EASE-model for piperazine is in Appendix 1 (EASE 3).

Dermal exposure during cleaning and maintenance

Dermal exposure to a substance, which is directly handled, is determined by the pattern (Wide dispersive use) and the contact level (Intermittent), resulting in an exposure range of 1-5 mg/cm^2/day. During cleaning and maintenance, it may be assumed that the equipment is rinsed with a suitable solvent or vacuum cleaned, leaving a portion (say 10%) of the original concentration, resulting in an exposure range of. 0.1-0.5 mg/cm^2/day. This is considered to be an infrequent exposure situation (4 hours/day).

The output from the EASE-model for piperazine is in Appendix 1 (EASE 5).

The exposure to piperazine during the exposure to airborne salt can be calculated by multiplying the salt concentration with the fraction of piperazine in the salt. The modelled exposures to piperazine salts by EASE are listed in **Table 4.11**.

Table 4.11 Piperazine dermal (mg/cm²/day) at the production of piperazine salts generated by EASE. The exposures of piperazine are calculated from the exposure to the salt dust (generated by EASE) and the fraction of piperazine in each salt.

Piperazine salt	Piperazine dermal exposure during loading, (assuming an exposure of 0.1-1 mg/cm²/day) 8-hour TWA	Piperazine dermal exposure during cleaning/maintenance, (assuming an exposure of 0.1-0.5 mg/cm²/day) 4-hour exposure
Adipate (37%)	0.037-0.37	0.037-0.18
Citrate (35%)	0.035-0.35	0.035-0.18
Dihydrochloride (50-53%)	0.050-0.50	0.050-0.25
Hexahydrate (44%)	0.044-0.44	0.044-0.22
Hydrochloride (48%)	0.048-0.48	0.048-0.24
Phosphate (42%)	0.042-0.42	0.042-0.21

4.1.1.3.4 Conclusion. Scenario 2 Industrial use of piperazine

The highest exposure to piperazine at sites using piperazine is assumed to be during the "loading", "final handling" and during "cleaning and maintenance". The other steps in the process are assumed to be closed and the release of piperazine to the working environment is probably low during normal conditions.

Dermal exposure at the industrial use of piperazine, where the piperazine free base is handled is assumed to be negligible as personal protective equipment (PPE) is assumed to be used because of the corrosive properties of the substance. However dermal exposure to the piperazine salts may occur where the salts are handled ("final handling").

2A. Production of piperazine salt

Considering all available data for exposure during production of piperazine salt from piperazine flakes a RWC for exposure, during loading, via inhalation is estimated to be 3.6 mg/m^3 (vapour) (8-hour TWA), 5.0 mg/m^3 (dust), giving a total of 8.6 mg/m^3.The corresponding exposure during loading of piperazine in aqueous solution gives a RWC, via inhalation, of 3.6 mg/m^3 (vapour) (8-hour TWA).

A RWC for exposure, during cleaning and maintenance, during production of piperazine salts from piperazine flakes via inhalation is estimated to be 5 mg/m^3 (dust) (4-hour TWA). The corresponding exposure during cleaning and maintenance, at the production of piperazine salts from piperazine in aqueous solution via inhalation is estimated to be 72 mg/m^3 (vapour) (4-hour TWA).

The exposure via inhalation during "final handling" is assumed to be 2.5 mg/m^3 (piperazine dihyhrochloride dust) (8-hour TWA) and for dermal exposure to be at 0.50 mg/cm^2/day (piperazine dihyhrochloride) on a skin area of 420 cm^2.

Typical exposure during production of piperazine salts is assumed to be 10% of the RWC both for exposure via inhalation and dermal exposure. Short-term exposure for 15 minutes is assumed to be 200% of the RWC.

2B. Synthesis processes with piperazine

Considering all available data for exposure during syntheses processes with piperazine flakes a RWC for exposure, during loading, via inhalation is estimated to be 3.6 mg/m^3 (vapour) (8-hour TWA), and 5.0 mg/m^3 (dust).

The corresponding exposure during loading of piperazine in aqueous solution gives a RWC, via inhalation, of 3.6 mg/m^3 (vapour) (8-hour TWA).

A RWC for exposure, during cleaning and maintenance, during synthesis processes with piperazine from piperazine flakes via inhalation is estimated to be 5 mg/m^3 (dust) (4-hour TWA). A RWC for exposure, during cleaning and maintenance, during synthesis processes with piperazine in aqueous solution via inhalation is estimated to be 72 mg/m^3 (vapour) (4-hour TWA).

Typical exposure during synthesis processes with piperazine is assumed to be 10% of the RWC both for exposure via inhalation and dermal exposure. Short term exposure for 15 minutes is assumed to be 200% of the RWC.

2C. Formulation with piperazine salts (dihydrochloride)

Considering all available data for exposure during loading of piperazine salts (dihydrochloride), a RWC for exposure, via inhalation is estimated to be 2.5 mg/m^3 (dust), (8-hour TWA) and for dermal exposure to be at 0.5 mg/cm^2/day on a skin area of 420 cm^2.

Considering all available data for exposure during cleaning and maintenance (piperazine salts), a RWC for exposure via inhalation is estimated to be 2.5 mg/m^3 (dust)(4-hour TWA) and for dermal exposure to be at 0.25 mg/cm^2/day on a skin area of 1,300 cm^2.

However, the values for cleaning and maintenance will not be brought forward to the risk characterisation for neither of these scenarios, as it is possible that cleaning are duties performed by the normal work staff and thus could be part of the other exposure estimates above.

4.1.1.3.5 Industrial end use of piperazine, Scenario 3

General discussion

Industrial end-use of piperazine occurs in, e.g., gas-washer formulations, as raw material/intermediate in chemical synthesis, and as hardener in glues. However, as there is a lack of information on how a considerable part of the produced piperazine is used by industry, it is possible that other uses occur as well. All products intended for industrial use containing piperazine may lead to human exposure. Hence, the extent of exposure may potentially be high and multiple routes of exposure may occur. It is envisaged that the work practices for the end-use of semi-manufactured products and end- products by professionals may be activities resulting in occupational exposure.

For the use of piperazine in gas-washer formulations, there is sufficient data for estimation of exposure. In contrast, no measured exposure data of piperazine in workplace air at other industrial end-uses of piperazine have been submitted, and enough data to allow EASE-estimation of the inhalation and dermal exposure is not available. Except for the gas-washers, no data of the number of sites were industrial end-use of piperazine are taking place are available.

Although exposure is likely to be very low in many circumstances, especially where formulations with low concentrations of piperazine are used at low temperatures, where no aerosol is formed, or when piperazine is part of chemical reactions in the products (e.g., in glues), there is no clear evidence that worst-case exposure during aerosol forming activities (e.g., gas washers) would be lower than for the industrial use of piperazine.

The release of piperazine from products containing piperazine depends on:

- the concentration of piperazine in the product.
- the mobility of piperazine in the matrix.
- the relative surface area of the product. The relative surface area depends on the conformation of the matrix and the use of the product.
- physical conditions of the surrounding media.

The exposure at workplaces when handling products and semi-products are likely to be lower than the exposure at the handling of the pure substance. Therefore, exposure via most products is assumed to be neglible, and the only scenario that has been assessed is the use of piperazine in gas-washers. There are no indications from any sources that other uses lead to any significant exposure.

Use of piperazine in gas-washer, Scenario 3.

Measured data for exposure during end use of piperazine in gas washer, Scenario 3

Table 4.12 Measured exposure data for piperazine in gas washer plants.

Year	Substance, activity	Concentration TWA mg/m^3 (sampling time)	Comment	Reference
1999	Filling unit	0.014 0.053	Personal sampling	(BASF AG, July 1999)
1999	Pump seal	0.0073 0.0063	Stationary sampling at customer	
1999	Condensing vessel	2.3	"	
1999	Storage tank/Vent flue/Vent	0.37	"	

No data on dermal exposure during end use of piperazine in gas washer has been provided.

Modelled data for exposure during use of piperazine in gas washer, Scenario 3

Inhalation exposure during loading

Inhalation exposure to the gas, vapour or liquid aerosol of piperazine at a process temperature of 20 is determined by: the pattern of use (Non-dispersive use), the pattern of control (LEV) and the ability of the substance to become airborne (low) resulting in an exposure range of 0.5-1.0 ppm (1.8-3.6 mg/m^3).

Dust exposure to a non-fibrous solid is determined by: the process operations (Dry manipulation), whether the solid aggregates readily (No) and the pattern of control (LEV present), resulting in an exposure range of 2-5 mg/m^3

The output from the EASE-model for piperazine is in Appendix 1 (EASE 1, EASE 2).

Inhalation exposure during cleaning and maintenance

Dust exposure to a non-fibrous solid is determined by: the process operations (Dry manipulation), whether the solid aggregates readily (No) and the pattern of control (LEV absent), resulting in an exposure range of 5-50 mg/m^3. During cleaning and maintenance, it may be assumed that the equipment is rinsed with a suitable solvent or vacuum cleaned, leaving a portion (say 10%) of the original concentration, resulting in an exposure range of 0.5-5 mg/m^3. This is considered to be an infrequent exposure situation, occurring every 3-5 years for a period of 8 hours per day for a few days at each occasion.

The output from the EASE-model for piperazine is in Appendix 1 (EASE 4).

Dermal exposure during loading

Dermal exposure in this scenario is assumed to be negligible as personal protective equipment (PPE) is assumed to be used because of the corrosive properties of the substance.

Dermal exposure during cleaning and maintenance

Dermal exposure in this scenario is assumed to be negligible as personal protective equipment (PPE) is assumed to be used because of the corrosive properties of the substance.

4.1.1.3.6 Conclusions. Scenario 3. Industrial end use of piperazine,

The highest exposure to piperazine at gas washer sites is assumed to be during the "loading" and during "cleaning and maintenance". The other steps in the process are assumed to be closed and the release of piperazine to the working environment is probably low during normal conditions.

Considering all available data for exposure during loading of piperazine flakes, a RWC for exposure, via inhalation is estimated to be 3.6 mg/m^3 (vapour), and 5.0 mg/m^3 (dust) (8-hour TWA). Considering all available data for exposure during cleaning and maintenance (flakes), a RWC for exposure, via inhalation is estimated to be 5.0 mg/ m^3 (dust) (8-hour TWA). The cleaning occurs every 3-5 years for a period of 8 hours per day for a few days at each occasion. However, as stipulated by the TGD (see Section 2.2.2.9), cleaning and maintenance occurring during stand-stills should not be brought forward to the risk characterisation.

4.1.1.3.7 Exposure control

Qualitative description of production, formulation and processing of piperazine indicates that both technical and personal protective measures are used. However, reliable documentation to demonstrate the reliability and representativeness of these data are not available.

To determine that protective measures maintain piperazine levels at a relatively low level, reliable and representative data are necessary. The available monitoring data are considered inadequate to fulfil this requirement.

4.1.1.3.8 Occupational exposure-Internal exposure

The following method for calculation of inhalation exposure has been used.

The occupational internal exposure by inhalation can be calculated:

$$U_{inh} = \frac{B_{inh} \times C_{inh} \times V_{inh}}{BW}$$

Values used for the calculation of inhalation exposure to airborne piperazine are as follow:

- U is the uptake (mg/kg/day)
- B_{inh} the bioavailability for inhalation exposure (100%/100)
- C_{inh} the air concentration (mg/m^3)
- V_{inh} the inhalation rate (10 m^3/day)
- BW the body weight of a worker (70 kg)

The following method for calculation of dermal exposure has been used

The occupational internal exposure by dermal absorption after exposure to piperazine can be calculated, using the following formula:

$$U_{derm} = \frac{B_{derm} \times C_{derm} \times S_{derm}}{BW}$$

Values used for the calculation of exposure to undiluted piperazine are as follow:

- U is the estimated total uptake (mg/kg B.W/day)
- BW the body weight of a worker (70 kg)
- S_{derm} the surface area of exposed skin
- C_{derm} is the amount of piperazine per skin area unit and day (mg/cm^2/day)
- B_{derm} is the bioavailability for dermal absorption of the daily external exposure of piperazine (100%/100).

4.1.1.4 Conclusion-occupational exposure to piperazine

Only a few data on occupational exposure was submitted. The uncertainties in the methods for sampling and analysis used, and the background information due to the circumstances in which the measurements were taken or the number of measurements was not well documented. For that reason the data was not used explicitly in the risk assessment. However, the measured values can be used for comparison to modelled values.

In the calculation of internal exposure, 100% bioavailiblity are used for all routes of exposure.

The 100% bioavailibility according to dermal absorption is probably an overestimation. This will be further discussed in the risk characterisation.

The occupational exposure is assessed without taking account of the possible influence of personal protective equipment (PPE). Data from the producers indicates that both technical measures and PPE are often used, and encompasses protective goggles, footwear and gloves (of vinyl or neoprene). Additional use of dust masks or supplied-air respiratory equipment may occur. No data on the efficiency of these measures are available. This will be further discussed in the risk characterisation.

Although attempts have been made to calculate exposure during cleaning and maintenance, it is acknowledged that the resulting figures probably overestimate the exposure. In addition, it is possible that cleaning and maintenance is performed by the normal work staff, already covered by the exposure estimates for normal duties. Therefore, cleaning and maintenance

will not be brought forward to the risk characterisation, but the exposure-values can be found in **Table 4.13** below.

There is little measured information on short-term exposure levels in the different scenarios. It has therefore been assumed that short-term exposure (15 minutes peak values) may be twice the RWC-value. Thus, for short-term exposure, the values would be twice the values in the first two columns of **Table 4.13**, and the short-term values are therefore not introduced in the table. These peak exposures are not expected to affect the total daily internal exposure, but they may increase the potential for, e.g., dermal and respiratory sensitisation.

Table 4.13 Summary of exposure levels for occupational exposure scenarios

Scenario	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	.		0.4	.	0.4	0.03-1.2
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	0.4	3	3.4	0.01-2.4
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	0.25	1300	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 neglible 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.

Note Loading and final handling activities are assumed; to last for 8 hours, the calculated exposed skin area is 420 cm^2 as worst case. Cleaning/maintenance activities are assumed to last for 4 hours, with the exception of Scenario 3, where it is assumed to last for 8 hours per day. The calculated exposed skin area is 1,300 cm^2 as worst case for cleaning and maintenance.

4.1.1.5 Consumer exposure

No quantitative data could be obtained for the evaluation of consumer exposure, neither from the chemical industry, nor from the literature.

There is no information indicating that piperazine as such is available to consumers, however, piperazine may be used in products (see Section 2.2.1) some of which are available to consumers.

There are very few useful data on the potential exposure from consumer products.

Data, which (if available) are used for a consumer exposure assessment, are actual exposure data, results from mathematical models for consumer exposure and empirical measurements of migration.

Any foreseeable misuses of piperazine have not been identified.

The routes of exposure will include inhalation, dermal oral and possibly combinations of these routes. No data on consumers' dermal exposure to piperazine are available. However this is assumed to be negligible.

4.1.1.5.1 Anthelmintic

Exposure to the general population seems to be mainly confined to the use of piperazine as anthelmintic.

Piperazine citrate can be used against both large roundworm (*Ascaris lumbricoides*) and pinworm (*Enterobius vermicularis*). A number of substituted piperazine derivatives are active in this respect, but only diethylcarbamazine has found wider clinical use. Piperazine is given orally usually for two days for the large roundworm, and for 7 days to treat pinworms. It causes flaccid paralysis of the parasites due to failure of the musculature to respond to acetylcholine, whereby they are dislodged from the digestive tract but are still alive when they are excreted (Saz and Bueding, 1966; Kirk-Othmer, 1992).

The recommended dose is 50-100 mg/kg for adults, and 50 mg/kg in children, giving a total maximum dose of about 4 g in four days (White and Standen, 1953).

Exposure via food from treated animals (meat and egg)

Indirect exposure from piperazine residues present in meat due to treatment of livestock (Morrison, 1997), as well as in eggs from treated hens (Leuenberger et al., 1986), may occur. Whereas the major part of these residues appears to be unchanged piperazine, a significant portion thereof consists of unidentified metabolites (Morrison, 1997).

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 in the risk characterisation.

4.1.1.6 Indirect exposure via the environment

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

No data on piperazine in breast milk are available.

Measured data for food

No measured data on occurrence of piperazine in food could be found.

4.1.1.6.1 Modelled

The EUSES program includes a model on the concentration of a chemical in biota, which has relevance for the food chain.

Intake can be determined based on the information of the concentration in the food and the intake data such as in EUSES. The indirect exposure of humans to piperazine originates from several sources. The exposure assessment (EUSES) includes six pathways: drinking water, fish, crops, meat, milk and air. The daily dose for humans is calculated by means of the concentrations in these media and the daily intake values. The default consumption rates for each food product are given. These values represent the highest country-average intake across all EU Member States for each food product.

Exposure is calculated based on daily intake of different foods, water and air. For adults, a body weight of 70 kg and inhalation rate of 20 m^3/day is used.

Table 4.14 Daily human intake of drinking water, different foodstuff and daily inhalation rate.

Parameter	Value Adult	Unit
Daily intake of drinking water	0.002	m^3/day
Daily intake of fish	0.115	kg_{wwt}/day
Daily intake of leaf crops (incl. fruit and cereals)	1.20	kg_{wwt}/day
Daily intake of root crops	0.384	kg_{wwt}/day
Daily intake of meat	0.301	kg_{wwt}/day
Daily intake of dairy products	1.333	kg_{wwt}/day
Daily inhalation rate	20	m^3/day
Body weight	70	kg

Piperazine may be released to the environment through wastewater and air effluents from manufacture, formulation, processing, use and disposal of piperazine containing products. These indirect exposure routes are described in Section 3.1.1.3.

The human intake from indirect exposure via food, water and air, both in local and regional scenarios are calculated with the EUSES-model and calculations according to the TGD and are presented in the **Table 4.15** below.

Exposure of humans via inhalation of air may be caused by emissions of piperazine to the environment from different life-cycle steps, see Section 2.1.

Multiplying the concentrations in the intake media by the daily intake rate of each medium and summing the contribution of each medium estimate the total daily intake.

Table 4.15 Predicted concentration in intake media and the total daily intake via the environment

Local Scenario		Drinking water (surface water) (mg/l)	Fish (mg/kg)	Leaf crops (mg/kg)	Root crops (mg/kg)	Meat (mg/kg)	Milk (mg/kg)	Air (mg/m^3)	Total local daily intake (mg/kg bw/day) Adult
A	Production	0.003	0.010	0	0	0	0	0	$3.5 \cdot 10^{-5}$
C	Production	0.05	0.20	0	0	0	0	0	0.002
E	Processing	0.0016	0.006	0	0	0	0	0	0
F	Processing and formulation	0.0016	0.006	0	0	0	0	0	0
G	Processing and formulation	0.0026	0.01	0	0	0	0	0	$3.5 \cdot 10^{-5}$
H	Formulation	0.24	1.0	0	0	0	0	0	0.008
EUSES Scenario 6	Gas washer	0.61	1.18	0.032	0.567	$2.83 \cdot 10^{-5}$	$2.83 \cdot 10^{-3}$	$3.45 \cdot 10^{-4}$	0.189
EUSES Scenario 7	Private use pharmaceuticals	$1.37 \cdot 10^{-3}$	$5.34 \cdot 10^{-3}$	$9.98 \cdot 10^{-7}$	$2.64 \cdot 10^{-6}$	$5.98 \cdot 10^{-8}$	$5.98 \cdot 10^{-7}$	$1.14 \cdot 10^{-8}$	$7.97 \cdot 10^{-7}$
EUSES Scenario 8	Groundwater-Manure from piperazine treated animals	0.02	$2.67 \cdot 10^{-3}$	$3.6 \cdot 10^{-3}$	0.9	$1.4 \cdot 10^{-6}$	$1.4 \cdot 10^{-5}$	$9.51 \cdot 10^{-9}$	$2.94 \cdot 10^{-8}$
Regional (EUSES)		$1.76 \cdot 10^{-5}$	$3.59 \cdot 10^{-6}$	$1.52 \cdot 10^{-8}$	$1.7 \cdot 10^{-8}$	$1.16 \cdot 10^{-10}$	$2.16 \cdot 10^{-9}$	$2.9 \cdot 10^{-9}$	$2.16 \cdot 10^{-5}$

* Site B and site D are located at the sea and at an estuary and are therefore not assumed relevant for assessment of human exposure via the environment.

The predominant sources of human exposure to piperazine via the environment are via drinking water (the major part), with minor contributions from fish and root crops, in all scenarios except for EUSES Scenario 8; Manure from piperazine treated animals. For this scenario, root crops are the major source (88%) and water a small contributing source (10%).

The regional total daily intake in humans is calculated by EUSES to $2.4 \cdot 10^{-5}$mg/kg/day.

The calculations methods are simple methods for predicting indirect exposure. Owing the considerable uncertainties accompanying the methodology, they serve primarily as screening methods.

A possible exposure route to humans is via groundwater contaminated to piperazine via the use as anthelmintics in domestic animals (see calculation in Section 3.1.4.1.1). The resulting

local concentrations in groundwater are 0.020 and 0.010 mg/l, under grassland and agricultural soil, respectively.

4.1.1.6.2 Exposure via out-door air

Inhalation of air out-doors may cause human exposure to piperazine, caused of the emissions from the industry handling piperazine and materials containing piperazine used in the society. Exposure to piperazine via inhalation of ambient, out-door air is generally considered a minor source. Piperazine in the atmosphere can either be adsorbed to particular matter or be in the vapour phase. The concentration and the human exposure to piperazine via air have been calculated with EUSES. The results are summarised in **Table 4.15**.

4.1.1.7 Multiple routes

The exposure to piperazine can be by different routes - inhalation, dermal, and oral. In some cases the individual may be exposed by more than one route at the same time.

Some of these situations are identified:

- Occupational exposure (inhalation and dermal) when handling the pure substance or salt during manufacture and formulation.
- Consumers exposure (oral)
- Indirect exposure via the environment (inhalation and oral)

4.1.1.8 Combined exposure

Due to the use of piperazine in the society and the diffuse emissions from products, humans may be exposed from different sources (mentioned in Section 4.1.1.1). The total exposure (body burden) is the sum of all the specific exposures, but all sources of human exposure to piperazine have perhaps not been identified. No information is available for estimation of peak exposures, frequency and duration. This makes it difficult to calculate a total combined exposure.

4.1.2 Effects assessment: Hazard identification and Dose (concentration) - response (effect) assessment

For most endpoints, there are no studies dealing with piperazine as such. However, piperazine hexahydrate, as well as different salts of piperazine have been used in the various studies cited in this RAR. In an aqueous solution piperazine is a fairly strong base, implying a high degree of dissociation of its salts with acids like hydrochloric, phosphoric and the relatively strong organic acid, citric acid. Besides pH-related effects, there are also differences in solubility of the different salts. There may therefore be some differences in bioavailability, e.g., after dermal exposure. However, there are no indications in the database that these derivatives differ significantly with respect to toxicological properties. It has therefore been considered justified to use toxicological data also for the salts of piperazine as a basis for this evaluation.

4.1.2.1 Toxico-kinetics; uptake, distribution, metabolism, and excretion

Whereas a considerable effort has been devoted to the formation of nitrosated compounds from piperazine, less is known about the uptake, distribution, metabolism and excretion of piperazine as such. Thus, no studies providing information on dermal or respiratory uptake have been located.

4.1.2.1.1 Studies in animals

Key study

The absorption, distribution and excretion of piperazine dihydrochloride have recently been studied in pigs (Morrison, 1997). By gastric intubation, two male and two female pigs were administered a single dose of ^{14}C-piperazine at a nominal dose of 300 mg/kg bw and the excretion of radiolabeled material in urine and faeces was followed for up to 7 days in two animals, and two were sacrificed 12 and 24 hours after dosing for determination of radiolabel in liver, kidneys, muscle, fat and skin. Peak plasma concentrations were attained 1 hour after administration, followed by rapid disappearance from the blood. 56% of the total activity was eliminated via urine during 7 days, out of which 46% was excreted in the first 24 hours. During the time of observation, 16% was excreted in faeces, while; again, most of the dose (8%) was eliminated during the first 24 hours. When residues present in cage debris and washes are also included, after 7 days about one fourth of the totally administered amount can be considered as still retained in the body. Of the sampled tissues, the highest activity was found in kidneys and liver. However, whereas elimination of the activity in kidney was rapid, with only some 3% remaining of the 12-hour value post dosing, the excretion from liver, skeletal muscle, fat and skin was considerably slower with 10, 11, 24, 25%, respectively, remaining after 7 days in comparison with the 12-hour levels. There is no information concerning enterohepatic circulation or biliary excretion. By means of thin layer chromatography (TLC), high performance liquid chromatography (HPLC), and by liquid chromatography-mass spectroscopy (LC-MS) attempts were made to characterise the labelled material present in urine, faeces, as well as in tissues, and was mostly found to initially consist of unchanged piperazine. In the urine collected 0-24 hours, 82-83% of the peak activity co-chromatographed with piperazine in HPLC or TLC. By the use of LC-MS for the radioactive residues found in tissue, the validity of the results from the chromatographic analysis could be confirmed, although there were some discrepancies between the HPLC and the TLC data. The nature of the labelled conversion products derived from piperazine was not determined, and the proportion of such metabolites in the urine increased with time to reach about 40-50% of the remaining activity in the 144-168 hour urine as judged by HPLC and TLC. In the kidney the fraction unidentified metabolites increased from about 20% at 12 hours post dosing to 80-90% of the remaining activity at 96 hours post dosing. Since carbon dioxide in exhaled air was not collected, minor metabolic conversion of piperazine to this metabolic end product cannot be excluded.

Supporting data

After oral administration of piperazine citrate to hens at a dose of 0.9 g per hen, an elimination half-life of 29 hours was determined by means of HPLC of the dansylderivative after clean up by TLC. A maximum level of 1.5 mg piperazine/kg egg was found two days post dosing. No determination of metabolites was carried out (Leuenberger et al., 1986).

An early attempt to identify the metabolites from C-14 labelled piperazine in poultry and swine indicated that the metabolites were similar in both species, as well as that piperazine was metabolised largely to labelled products that were found to be associated with polysaccharides, hexoses and to a lesser extent to amino acids (Rutter and Voelker, 1975), probably as a result of metabolic incorporation of labelled breakdown products. Also, identification of the labelled metabolites was carried out by comparison with R_f standards utilising TLC, and the conclusions therefore need verification by other methods. Furthermore, whereas only "trace amounts" were reported to be found in animal tissues 24 hours post dosing, a subsequently more thoroughly conducted study in swine (Morrison, 1997) found 23% of the administered labelled material to be retained after 7 days (see above).

Nitrosation of piperazine

Nitrosation of piperazine to N-mononitrosopiperazine (NPZ) in the presence of nitrite is a rapid reaction, whereas the di-nitrosoderivative is formed at a slower rate. In dogs fed high levels of piperazine (3 g) plus nitrite (400 mg), nitrosation of the amine was reported to take place *in vivo*, with the excretion of N,N'-dinitrosopiperazine (DNP) (Sander et al., 1973; Sander et al., 1975). Sander et al. (1975) could only detect very small amounts of DNP (less than 1% conversion) in the stomach of the rat formed from the combined administration of piperazine and nitrite at a dose of about 25-50 mg/kg.

Hecht et al. (1984) claimed, on the other hand, a yield of 38% DNP from feeding a single dose of 13 mg of nitrite and 1.7 mg of piperazine to rats. However, this was not based on direct determination of the di-nitroso compound, but relied on the unverified assumption, that the measured metabolites, N-nitroso(2-hydroxyethyl)glycine, N-nitrosodiethanolamine, as well as 3-hydroxy-N-nitrosopyrrolidine solely originate from N,N'-dinitrosopiperazine.

Subsequently, Tricker et al. (1991) demonstrated that N-nitrosodiethanolamine, as well as 3-hydroxy-N-nitrosopyrrolidine are indeed also metabolites of NPZ. It is important to note, that the nitrosation rate is proportional to the square of the nitrate concentration, implying a rapidly decreasing yield with decreasing concentrations and in the presence of reducing agents, like ascorbic acid, the yields are appreciably reduced further (Sander et al., 1975). Also, whereas the pH of the rodent stomach lies close to the pH optimum for nitrosation of amines (Mirvish, 1982), this is not so for the human stomach with its considerably higher acidity. Finally, the nitrite doses used in these experiments must be considered as unrealistically high in as much as the nitrite load for the adult man has been estimated at about 1.1-1.7 mg/kg by Tannenbaum (1978), although more recent estimates give considerably lower values with means in the range 0.04-0.06 mg/kg (Fernlöf and Darnerud, 1996). Thus, the nitrite load for a 70 kg human will lie orders of magnitude below those used in the above-cited rodent studies.

The trace amounts of mononitropiperazine in the range 0.06-0.08 ppb (E. Martinsson, Akzo-Nobel, personal communication) present in commercial piperazine must be considered to lack significance in this context.

4.1.2.1.2 Studies in humans

Upon oral administration to humans of piperazine salts, there were wide individual variations in the rate of excretion with urine, where approximately 15% of the dose was excreted with urine within 5 hours, and 30% after 24 hours (Rogers, 1958). Analysis of piperazine was based on a colorimetric method using 1,2-naphtoquinone-4-sulfonic acid (Folin's amino acid

reagent) that is not specific for piperazine, and no inference can be made with respect to the presence of metabolites.

Using a similar colorimetric method, the excretion of piperazine with urine was studied in five human subjects administered a single oral dose of 3.5 g piperazine citrate. Within 24 hours between 60 to 75% of the administered dose was excreted (Hanna and Tang, 1973). The total recovery in urine collected during 24 hours varied from 15 to 75%.

When 480 mg piperazine was administered to 4 volunteers, during a period of 16 hours, 19-35% of the administered dose was recovered as unchanged piperazine in urine, with 2-3% excreted over an additional period of 24 hours (Bellander and et al., 1985).

No information on excretion of piperazine in man with faeces has been located.

Generation of N-mononitrosopiperazine

Generation of NPZ in quantities ranging from 0.08 to 0.59 µg/ml could be detected in gastric juice from human volunteers given a single dose of 480 mg piperazine orally. Up to 4.7 µg NPZ was excreted in urine over a period of 24 hours (Bellander et al., 1981). The authors later estimated, that the highest total amount of NPZ that could have been formed was in the order of 50 µg (Bellander et al, 1987), i.e. a conversion efficiency of about 0.01%. However, the dinitroso compound could not be detected (detection limit, 0.004 µg/ml) in either gastric juice, blood, or in urine. In view of the fact that Hecht and co-workers (Hecht et al., 1984) have claimed that about 20% of a single oral dose of DNPZ is excreted as unchanged DNPZ, the formation rate of the more potent carcinogen, DNPZ, from piperazine must have been very low in these individuals.

In a subsequent study, NPZ could be detected in the urine from exposed workers, where the time-weighted average concentration of piperazine in the breathing zone over 12 hours was <0.03-1.7 mg/m^3. The total amount of NPZ excreted with urine was 0.7-4.7 µg/person per 2 hours. Also in this case, no DNPZ was detected (Bellander et al., 1987). The total excretion of piperazine in urine during exposure and after 12 hours was 70-4,700 µg/person. Adjusted for excretion of a maximum of 38% of the absorbed dose as unchanged piperazine as found by Bellander et al. (1985), the amount taken up would then correspond to 184-12,400 µg, which could indicate a higher rate of conversion for chronic exposures to lower doses, but where the efficiency of NPZ formation decreases with increasing uptake. Using a conservative estimate of 1% conversion for the highest exposure, a maximum generation of 124 µg NPZ is obtained. Within a factor of two, this is in reasonable agreement with the finding, that 10.5% of a dose of NPZ administered to the rat was found to be excreted unchanged in urine (Tricker et al., 1991). See further Sections 4.1.2.8.3 and 4.1.3.1.6.

4.1.2.1.3 Summary of toxicokinetics

In the pig 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. An oral absorption of 100% is brought forward to the exposure assessment. However, no data on dermal or respiratory uptake have been located. Default absorption values of 100% are assumed for dermal and inhalatory exposure.

The principal route of excretion of piperazine and its metabolites is via urine, with a minor fraction recovered from faeces (16%). However, about one forth of a single administered oral dose is retained in the tissues after 7 days, some of which seems to consist of unidentified

conversion products. Besides N-mononitrosopiperazine, no other metabolites have been identified.

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, although the nature and extent of conversion to metabolites remains unknown.

In the presence of nitrite, the *in vivo* formation of small amounts of nitrosated products from piperazine has been demonstrated to occur in the gastrointestinal tract of experimental animals as well as in humans.

4.1.2.2 Acute toxicity

4.1.2.2.1 Studies in animals

Piperazine has a low acute toxicity in mammals.

Acute toxicity, with piperazine administered by inhalation, was investigated in Sprague-Dawley-rats (BASF, Gewerbehygiene und Toxikologie, 1980). Piperazine chips were filled in a glass flask, and placed in a water bath at 20^{o}C. Air was flown through the chips at a rate of 200 l per hour. The air stream, with dust particles and volatile piperazine, was passed through glass chambers with rats, in total 12 animals. The exposure time was 3, 10, 30 minutes, 1, 3 or 7 hours. The animals were observed for 14 days after the test. No animals died and no symptoms were found at autopsy. No piperazine concentration was given.

The acute oral LD50 in mice and rats has been reported to be in the range 2.4 to 4.3 g (expressed as piperazine base) per kg body weight (Cross et al., 1954; Martin, 1993). Most of the studies are of older date and do not fulfil GLP or the criteria contained in modern guidelines. However, one investigation conducted by BASF, which is of a quality comparable to a guideline study, is available (BASF AG, Department of Toxicology, (79/562) unpublished data of April 30, 1980). Piperazine “chips” were dissolved in an aqueous solution of 0.5% carboxymethylcellulose and given to groups of 5 male and 5 female Sprague Dawley rats at 1,000, 1,210, 1,780, 2,610, or 3,830 mg/kg bw and followed during 14 days post dosing. There were no mortalities at the three lower doses, and the approximate oral LD_{50} was 2,600 mg/kg piperazine base for both males and females.

In a study from 1954 the acute oral toxicities of the pure and technical adipates were compared with the technical piperazine hydrate in male albino mouse administered the compound in 5% mucilage of acacia by gavage. Expressed as piperazine base, the LD_{50s} were for the three preparations: 4.2, 3.0, and 1.9 g, indicating a slight difference (Cross et al., 1954).

The observation that intraperitoneal injection of a single dose of about 200 mg of piperazine base given to the guinea pig as the tripiperazine dicitrate caused death in tetanic convulsive seizures (Ratner et al., 1955), also deserves mentioning in view of similar reactions elicited by piperazine in felidae species (Rettig, 1981) and the fact that piperazine lowers the seizure threshold in human epileptics.

A Union Carbide Co. technical data sheet reports a dermal LD_{50} of 4 g/kg in rabbits (cited in Trochimowicz et al. 1994).

See also Section 4.1.2.6.1, where some of the studies cited under data gaps (neurotoxicity) only involve a few days of dosing, and thus could be considered as acute toxicity.

4.1.2.2.2 Studies in humans

Experience from the pharmaceutical use of piperazine indicates a moderate to low acute toxicity. Although no data on the lethal dose have been located, its use against gout at the end of the nineteenth century involved single doses that sometimes exceeded 10 g (corresponding to a dose of 144 mg/kg if assuming a body weight of 70 kg) (Stewart, 1894; Slaughter, 1896).

In Section 4.1.2.6.2, several studies describing neurotoxicity in humans after a few days of dosing are discussed. The majority of these cases involve administration of piperazine for 5-7 days. However, there is one case where horizontal nystagmus, generalised diminution of muscle power (she was quite unable to stand or sit without support), hypotonia and diminished tendon reflexes were observed in a 12-year-old girl given a single dose of piperazine citrate, corresponding to 24 mg/kg piperazine base (Bomb and Bedi, 1976). After 24 hours the symptoms had disappeared. Belloni and Rizzoni (1967) described a similar case involving three days of exposure of a 4-year-old child to 44 mg/kg piperazine base (i.e., totally 132 mg/kg). There is also one report (Padelt et al., 1966), which studied EEG changes in 89 children one day after administration of two doses (12 hours apart) of piperazine hexahydrate, corresponding to a total 'daily' dose of 90-130 mg/kg piperazine base. Whereas no visible signs of neurotoxicity were observed in the children, significant pathological EEG effects were noted in 37% of them, including an EEG picture characterised by generalised pre-seizure potential.

Considering that piperazine has been used as an anthelmintic agent in the treatment of a very large number of people worldwide, and only two relatively severe cases have been reported after 1-3 days of exposure (to 24 and 132 mg/kg, respectively), it is possible that the sensitivity of these individuals has been increased by, e.g., kidney or liver malfunction, or perhaps some rare enzyme polymorphism. However, since EEG changes were observed in 37% of 89 children administered 90-130 mg/kg piperazine base (two doses during one day), these effects cannot be explained by extreme sensitivities. A plausible mechanism that may account for the EEG changes is the agonism at the GABA receptor proposed to be exerted by piperazine. In addition, there are 36 case descriptions of varying quality describing neurotoxicological symptoms after total doses of roughly 200 mg/kg piperazine base (divided during 5-7 days). Although there remains a possibility that children are more sensitive than adults, a LOAEL of 110 mg/kg for neurotoxicity in humans after acute exposure is proposed.

4.1.2.2.3 Summary of acute toxicity

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 located. The lethal dose in humans has not been established. However, there are findings of EEG changes in 37% of 89 children administered 90-130 mg/kg piperazine base (two doses during one day), corroborated by the proposed GABA receptor agonism exerted by piperazine. Since more severe neurotoxicity symptoms can appear after exposure to higher doses (divided under several days), a LOAEL of 110 mg/kg for neurotoxicity in humans after acute exposure is proposed.

4.1.2.3 Irritation

4.1.2.3.1 Studies in animals

Dermal

Piperazine is a strongly basic amine. In an acute dermal irritation/corrosion test conducted according to OECD Guideline 404, piperazine was found to be strongly irritating to the skin of white rabbits, strain "Weisser Wiener" (BASF, 1984): Two males and one female were kept individually and the fur was removed by close clipping at least 15 hours pre dosing. About 0.5 g of piperazine in a 50% aqueous solution (assumingly piperazine base) was applied to a 6.25 cm^2 gauze patch and applied to the skin and covered with a semi-occlusive dressing. After exposure for 4 hours, the test substance was removed, and the skin reaction evaluated after 30-60 minutes, 24, 48 and 72 hours, respectively. Severe erythema and necrosis was observed in all animals after 48 and 72 hours.

Eye

An aqueous solution containing 1-5% piperazine (assumingly piperazine base) caused etching and necrosis of the rabbit cornea (Carpenter and Smyth, 1946). Normal rabbit eyes were selected on basis of visual inspection after staining with a 5% aqueous solution of fluorescein, and flushed out with distilled water 20 seconds after application. After a 2-hour resting period, 0.005 ml of a 5% solution was applied to the centre of the cornea while the lids were retracted. About one minute later the lids were released, and 18-24 hours later the eyes were stained with fluorescein and the injury scored. Together with sulphuric acid and ammonium hydroxide, piperazine was given the grade 9 on a scale ranging from 1 to 10, with necrosis covering 60-90% of the cornea.

4.1.2.3.2 Studies in humans

Application of a 25% aqueous solution of piperazine hexahydrate (25 g piperazine hexahydrate/ 100 ml water, equivalent to 11% piperazine base) caused primary dermal irritation in 10 out of 12 human volunteers, whereas concentrations below 50 g/L (<5% piperazine hexahydrate, equivalent to < 2.2% piperazine base) had no visible adverse effects (McCullagh, 1968b). Patches soaked with the test solution were applied to the skin for periods up to 48 hours. There was a significant difference between two sources of the hexahydrate in as much as the product from one source seemed more irritating than the other. The responses varied from no response to erythema and marked vesiculation.

4.1.2.3.3 Summary of skin and eye irritation

In rabbits, a 50% aqueous solution of piperazine base (i.e., piperazine anhydrate) has strongly irritating properties, including induction of skin necrosis. At a concentration of 11%, piperazine base may induce erythema and marked vesiculation on human skin, whereas no effects were observed at a concentration < 2.2% piperazine base.

Piperazine base may cause etching and necrosis of the rabbit eye at a concentration of 1-5%.

4.1.2.4 Corrosivity

Piperazine base (i.e., the anhydrate) and piperazine hexahydrate should be regarded as corrosive with respect to the eye based on etching and necrosis caused by 1-5% solution of piperazine base in the rabbit eye (Carpenter and Smyth, 1946). Existing biological data on the corrosive properties of piperazine are corroborated by its high pH in aqueous solutions (See Section 1.3.13). Piperazine is currently classified with R34, which applies for piperazine base and piperazine hexahydrate. No corrosivity is expected for piperazine salts.

4.1.2.5 Sensitisation

4.1.2.5.1 Studies in animals

Piperazine (68% aqueous, not further defined) was recently studied in the Local Lymph Node Assay (LLNA). Groups of young adult Balb/c mice (n=5) were administered 25 µl piperazine in water/acetone/olive oil (10:4:1)(water/AOO) at concentrations of 5, 10 and 20% (w/v) on the dorsum of both ears daily for three consecutive days. Control animals were treated with the vehicle alone (n=10, water/AOO) or with 1% DNCB (n=5) dissolved in AOO. Piperazine (10%) produced a weakly positive response as measured as ^{3}H-thymidine incorporation in lymph nodes five days after initiation of treatment. A lack of effect at 20% was probably caused by local irritation and corrosion at this concentration (Dearman and Kimber, 2001).

Cytokine production was also studied by Dearman and Kimber (2001). The mice were administered 50 µl piperazine in water/acetone/olive oil (10:4:1) (water/AOO) at concentrations of 5 and 10% (w/v) on each shaved flank at days 1 and 6. At days 11, 12, and 13, daily doses of 25 µl were applied to the ears. The cytokine production was measured 13 days after initiation of treatment. Cytokine production (IFN-γ) was demonstrated, supporting that piperazine possess contact allergenic potential in mice. In the same study, piperazine failed to provoke production of IL-4 and IL-10, which are normally thought of as markers of respiratory tract allergens.

In an attempt to investigate sensitising potential, piperazine citrate failed to elicit anaphylactoid reactions in the guinea pig upon intraperitoneal administration for nine days, followed by a challenge dose by intravenous injection 21 days later. Nor were any cutaneous reactions observed when piperazine was given subcutaneously with Freund's adjuvant, and subsequently challenged with a single dose of piperazine citrate, given either intracutaneously of intravenously (Ratner et al., 1955). Guinea pigs were each given 4 intraperitoneal or subcutaneous doses of the tripiperazine dicitrate corresponding to doses ranging from a total of 8 to 40 mg/kg expressed as piperazine base over a period of 9 days. 6-21 days later all animals were challenged with a single dose of 4 mg/kg piperazine. An attempt to elicit sensitisation by mixing piperazine citrate with Freund’s adjuvant, with subsequent intracutaneous challenge 20 days later (no details provided), was likewise negative. No positive controls were included, and the negative outcome of this old study cannot be accepted as evidence of lack of sensitising potential.

In a Guinea Pig Maximisation Test of technical diethylenetriamine Comm (DETA-COMM), 11 out of 20 animals challenged with technical DETA responded. When investigated for cross-sensitisation, one of the animals reacted to piperazine (25% in water) in the absence of irritation in the control, suggesting some degree of cross-sensitisation. Using diethylenetriamine-HP that exhibited a strong potential to induce dermal sensitisation (16 of

20), a clear cross-sensitisation to 25% piperazine (11 of 20 animals) was reported (Auletta and Daly, 1990). The above investigation was expanded, which showed that, among the ethylenediamines, piperazine (25% in water) it was a mild sensitiser affecting 5% of the animals (Lueng and Auletta, 1997).

4.1.2.5.2 Studies in humans

Allergic dermatitis

Similarly to amines, such as ethylene diamine, aminoethyl ethanolamine, 3-(dimethylamino) propylamine, and triethylene tetramine, piperazine and its salts have the potential to cause occupational asthma (reviewed by Hagmar (1986)) as well as allergic dermatitis. Below, a summary of published case reports is provided with respect to the latter:

Patch testing of a 1% piperazine solution on 93 patients on a clinic revealed 3.2% positive allergic reactions. The test strip was applied on the subject's back and left in place for 2 or 3 days. Readings of reactions took place immediately after removing and 2-3 days later. The scoring was based on the method of the International Contact Dermatitis Group. The study details are poorly reported. (Holness and Nethercott, 1997).

A 5 years old male child with no family history of allergic disorders was given two consecutive treatments with "Antepar Elixir" (piperazine citrate) for the treatment of pinworm. After a second round of treatments, urticarial erythematous swellings were observed, that increased to gross oedema, mainly in the areas of the face, eyelids, and penis. Upon cessation of the drug and administration of tripolidone and ephedrine, the reactions gradually subsided within 4 days (Hill, 1957).

A 37 years old Australian woman with no previous history of allergic reactions, developed a generalised erythematous and intensely pruritic rash some 45 minutes after ingestion of a dose of about 500 mg of piperazine citrate. Upon a second dosing, the reactions reappeared. When living in Hong Kong she had previously used piperazine containing anthelmintics without adverse reactions (Butler, 1968).

A 27-year-old woman working in a pharmaceutical laboratory developed hand eczema. She routinely packed "Carudolo" suppositories, which contained phenylbutazone-piperazine and semi-synthetic glycerides. The lesions remitted during holidays and week-ends but reappeared when she returned to work. Patch test results showed marked positive reactions against "Carudolo" suppositories, phenylbutazone-piperazine 1% pet. and piperazine (5% in water). The same investigator also reported a 71-year-old man that developed bilateral acute eczema after applying Carudolo gel for rheumatic pain. The lesions subsided within a few days after cessation of the treatment. Carudolo gel contained phenylbutazone-piperazine, methylnicotinate, piperazine hexahydrate carboxypolymethylene, diisopropanolamine, ethyl alcohol and water. A patch test showed marked positive reactions against Carudolo gel and piperazine (5% in water) (Menezes Brandao and Fousserau, 1982).

A 50-year-old woman worked in a pharmaceutical factory handling ampoules of drugs. She developed dermatitis on her hands and was patch-tested against the drug Thiodazine "Polfa" that contained thiourea and piperazine. A positive reaction was seen against the ampoule content and piperazine after 96 hours (but not after 48 hours) (Rudzki and Grzywa, 1977).

In 1963, Foussereau reported 9 French cases that had positive reactions against piperazine (5% in water). Nurses in a resuscitation unit became sensitive to piperazine through handling camphosulphonate of piperazine (Foussereau, 1963).

In 1973, a positive reaction against piperazine was found in a 49-year old man from Senegal. He was employed in a commercial kitchen and developed hand eczema. The piperazine source was not positively identified (Calas et al., 1975).

A 13-year-old boy developed chronic eczema on the ventral aspect of the forearm. The symptoms began when he started to wear a plastic watchstrap. In rubber patch test series he showed positive reactions to piperazine 1% pet. at 72 and 96 hours. A patch test with the plastic watchstrap was negative (Savini et al., 1990).

A 55-year-old man developed generalised dermatitis after use of Carudolo suppositories containing phenylbutazone-piperazine. In addition to anal irritation, erythema with mild itching spread over his body with a later scaling during one month. He had a personal, and a family history of atopy. Patch test results showed positive reactions against piperazine 1% water, phenylbutazone 5% pet. and some other pyrazoline derivatives (Fernandez de Corres et al., 1986).

As mentioned above, a study in the guinea pig has indicated cross-sensitisation between ethylenediamine and piperazine (Auletta and Daly, 1990), an observation that seems to be supported by clinical experience. Thus, in patients dermally sensitised to ethylene diamine (Burry, 1968; Price and Hall-Smith, 1984; Geier, 1995) cross-sensitisation to piperazine as well as to several other amines have been reported. Cross-sensitisation with pyrazoline derivatives has also been described (Fernandez de Corres et al., 1986).

A laboratory technician in a pharmaceutical company that developed a rash on his fingers with severe nail dystrophy, scored positive in patch testing for piperazine as well as ethylenediamine (Calman, 1975).

A 37-year-old man with a history of atopy developed generalised itchy morbiliform rash 12 hours after oral treatment with piperazine citrate against pinworm. A year after this incidence the same treatment was repeated and he developed a severe exfoliative erythroderma within three hours. He was challenged orally with 50 μg piperazine hydrate and developed maculopapular erythema within hours with shivering, anxiety and tachycardia. Subsequent patch tests showed positive reactions to ethylenediamine 1% (piperazine not tested) (Wright and Harman, 1983).

A 36-year-old man with a history of atopy developed generalised erythroderma, facial swelling and malaise 4 hours after oral treatment with piperazine phosphate against pinworm. Patch tests showed positive reactions to ethylenediamine 1% pet. and neomycin 20% pet. at 48 hours (piperazine not tested) (Price and Hall-Smith, 1984).

During 3 years, 50 cases of ethylenediamine sensitisation were recorded in an Italian dermatological clinic. 48 of the 50 patients had either used a cream containing triamcinolone acetonide, neomycin, gramicidin, nystatin and ethylenediamine, or an ointment containing halcinonide, neomycin, nystatin and ethylenediamine. When 22 of these patients were retested to piperazine 5% pet., among other compounds, 5 (22%) reacted positively to piperazine. (Balato et al., 1984).

The same Italian clinic later studied 32 ethylenediamine sensitive patients, and 29 of these patients could remember that they had previously used a topical product containing ethylenediamine. Two (6%) of the 32 patients reacted positively to piperazine 1% pet. (Balato et al., 1986).

Sensitisation of the Respiratory Tract

Key data from a series of studies of a cohort of Swedish workers

A series of systematic surveys of asthmatic reactions among workers exposed in a Swedish factory during production of piperazine anhydrate, and a number of salts (adipate, citrate, phosphate, and dihydrochloride) were undertaken (reviewed by (Hagmar et al., 1986).

Personal sampling was performed with all-glass, capillary-tip, 30-ml midget impingers containing HCl absorption solution. The flow was 1.5 L/minute, typically for 60 minutes. The sampling efficiency for particles larger than 0.8 μg has been documented to be high (Davies et al., 1951), and the capture of vapor was found to be very effective. At least 900 L of an atmosphere containing 2 mg/m^3 could be sampled without breakthrough to a second impinger.

The sample was evaporated to dryness and redissolved in NaOH. A 0.5 μL aliquot was injected on a 2 m column packed with 15% Carbowax 4,000 Special and 2% KOH on a chromatographic support (80/100 mesh Chromosorb W). The column temperature was 150°C; inlet, 230°C; and detector, 170°C. Standards were made up from a stock piperazine standard in 0.1 M HCl and concentrated in the same manner as the samples. With this method, the analytical recovery was claimed to be 85% in the range of 10 to 300 μg per sample. In the same range the precision of sample treatment and analysis was claimed to be ±31% (95% confidence interval). The detection limit was 3 to 10 μg per sample, corresponding to 0.03 to 0.1 mg/m^3 in a 60 minute sample. In itself the recovery check constitutes one kind of "validation" for an analytical procedure, which at that time was considered to represent the best available technique and carried out by a well-established and internationally well-known occupational health laboratory. There has been concern expressed with regard to the sampling method, and modern procedures could possibly yield more accurate data. However, there is at present no other quantitative information available to evaluate the sampling success in the Hagmar study.

Among the 131 workers directly employed in the production of piperazine in this factory 1979, where, in addition, potential exposure to several other chemicals also existed, information about work-related respiratory symptoms was obtained by a questionnaire administered through the factory medical health service, and spirometry was also conducted. Fifteen persons were classified as asthmatic, or had experienced symptoms of asthma during their work. Sixty-nine potential asthmatic cases could also be traced among 400 former workers. Telephone interviews with 58 of these persons revealed 18 additional cases of occupational asthma of which 13 had supporting medical records.

The criteria for the diagnosis of chemically induced asthma were recurrent dyspnoea with wheezing breathing and coughing, and an unequivocal association with exposure to a specific agent. The etiological agent was judged to be piperazine in 29 persons, and ethylenediamine in 3. None of the subjects had a history of attacks before employment, and atopic subjects were not preferentially affected. Specific provocation tests with piperazine were positive, whereas bronchial constriction was not provoked in asymptomatic control subjects.

The exposure was characterised as intermittent exposures, sometimes with months elapsing between exposures. The time lag between first exposure and onset of asthma could vary from months to years, and the asthmatic reactions were mostly of the delayed type, but in some cases there was also an immediate transient reaction that was followed by a prolonged late-phase reaction. In conclusion, occupational asthma was obviously a problem in this particular chemical factory, where the processing of piperazine, especially the anhydrate, appeared to constitute the cause (Hagmar et al., 1982).

Piperazine exposure scores were obtained for each subject expressed as a time-index (sum of time estimates for different work processes) and a time-weighted intensity index (sum of the products of each time estimate and corresponding intensity score, divided by the time index). Airway symptoms were clearly correlated with the piperazine time-index, but showed a less clear correlation with intensity of exposure. Operations generating the highest exposures were subsequently eliminated, and after more than one year a renewed study was undertaken.

In the second phase of investigations conducted in 1985, a detailed medical examination was performed including lung function tests, and the presence of specific IgE antibodies. A control group of 60 postal workers was selected, 72 out of 140 employees had been exposed to piperazine during the preceding year (Hagmar and Welinder, 1986). Five out of the exposed employees, but none out of 64 non-exposed factory workers and none out of the 60 postal workers, had specific lgE-antibodies against a conjugate of piperazine and human serum albumin as demonstrated *in vitro* using a radioallergosorbent test (RAST) and a RAST inhibition test. The authors interpreted the absence of IgE antibodies in some workers with symptoms of asthma in terms of pseudo-allergy or non-specific irritation (Welinder et al., 1986). However, whereas e.g. RAST techniques have been highly successful in detecting IgE mediated allergic reactions to high molecular weight allergens; this has not always been the case for low molecular weight occupational allergens. Thus, there are many individuals with chronic rhinitis or asthma in which it has not been possible to obtain proof of IgE-mediated allergy, a fact that does not necessary exclude an immunological background (Karol, 1992).

Eight out of the 72 exposed workers had a history of piperazine associated asthma where the induction time was between 6 and 168 months before onset of respiratory symptoms. The RAST-negative asthmatics had an induction time of less than 1 month. Operation of different mechanisms of piperazine-induced asthma could be the cause for this discrepancy. The industrial operation most commonly associated with the onset of asthma was when heated liquid anhydrous piperazine solidified on a cold drum and was barrelled manually. The mean TWA for this process was 1.2 mg/m^3, but peak values of about 100 mg/m^3 were found during cleaning. The most recent case of asthma associated with drum flaking was discovered in 1983, when the TWA exposure level for piperazine in air was 0.7 mg/m^3, whereas among the personnel manufacturing the hexahydrate, a process characterised by a TWA level of 0.3-0.4 mg/m^3, no cases of asthma were found to have been elicited. For the latter groups, analysis by multiple regressions was included of lung function measures (VC, FEV1, VTG, VTG/TLC), age, height, smoking habits, atopy and piperazine exposure.

A healthy worker effect cannot be excluded, in as much as some piperazine-exposed workers could have been exposed in a manner that favoured those able to tolerate piperazine exposure and the true LOAEL and NOAEL applicable to the general population could actually be lower than the reported 0.4 mg/m^3. (Hagmar et al., 1982, 1986, 1987; Hagmar and Welinder, 1986; Hagmar, 1986).

In summary, this series of studies of a cohort of Swedish workers, about one third of the workers in the group with the highest exposures, suffered from symptoms of asthma, and a dose-response relationship was evident for the studied cohort, and a TWA level for piperazine in air of 0.7 mg/m^3, but not 0.4 mg/m^3, was found to induce respiratory symptoms.

However, because some processes had been closed down, the intensity as well as peak exposures could only be roughly estimated for these processes, the LOAEL as well as NOAEL for asthma induction in this cohort is, therefore, associated with too much uncertainty to be brought forward to the risk characterisation (Hagmar, 1986). Still, it is clear that piperazine is a respiratory sensitiser, which will be dealt with in the risk characterisation.

Supporting data

A clear-cut case of delayed asthma-like reactions in response to exposure to piperazine in the preparation of sheep drench had previously been described by McCullagh in Australia (McCullagh, 1968a). A provocation test resulting in a severe delayed asthmatic attack that required prednisone treatment, and confirmed piperazine as the causative agent. The author also referred to unpublished observations that cases of respiratory sensitivity had occurred in chemical plants in Sidney, England and Sweden.

Similar observations in two occupationally exposed chemists were subsequently published in England, where the sensitised individuals suffered late asthmatic reactions readily provoked by piperazine hydrochloride, a reaction that could be completely inhibited by disodium cromoglycate (Pepeys et al., 1972). Skin prick tests using piperazine were negative.

A 55-year old man, who had worked 2 months in a factory, developed eczema on the hands, arms, face and penis. The symptoms disappeared during a 3-week holiday but reappeared when he returned to work. He also developed respiratory symptoms. The man left the factory and was patch-tested 2 years later with 1% piperazine in water. Respiratory symptoms and itching at the piperazine test site were seen the next morning. The respiratory symptoms disappeared after 5-6 hours. The test was strongly positive after 48 hours (Fregert, 1976).

4.1.2.5.3 Summary of sensitisation

Exposure to piperazine and its salts has been demonstrated to cause allergic dermatitis as well as respiratory sensitisation, but no NOAEL can be set as no threshold could be deduced from these studies. Dermal sensitisation is also shown by LLNA in mice. A cross-sensitisation between piperazine and diethylentriamine was observed in guinea pigs. Classification with R42, R43 is suggested for piperazine based on human observations, epidemiological studies, and animal data.

4.1.2.6 Repeated dose toxicity

4.1.2.6.1 Studies in animals

Key study

In a dietary study with piperazine in beagle dogs with dosage levels up to 3,692 ppm (approximately 122 mg/kg/day) for 13 weeks, no clear LOEL could be established (Rutter and Voelker, 1975): Piperazine dihydrochloride was administered to groups of 8 dogs (4 males and 4 females) at 92 (3 mg/kg/day), or 369 ppm (12 mg/kg/day) in the feed for the low and

intermediary dosage groups. For the high level group, piperazine was administered at 1,476.8 ppm (50 mg/kg/day) for week 1 trough week 5, and at 3,692.0 ppm from week 6 through week 13. A fourth group served as controls. The doses correspond to 1.5, 6, and 25 mg/kg/day piperazine base.

Appearance and behaviour, body weight changes, clinical laboratory data, ophthalmoscopic findings, organ weights, as well as gross and microscopic pathology were recorded. All animals were observed daily for appearance, behaviour, appetite, elimination, and signs of toxic or pharmacological effects. Individual body weights, food and test compound consumption were recorded weekly for the duration of the study. Clinical laboratory studies were performed on all dogs initially, and at 4 and 13 weeks. Gross pathology was performed on all dogs following sacrifice, and the following organ weights were measured for each sacrificed dog and the organ/body weight ratios subsequently determined: thyroid, liver, spleen, kidney, adrenal and testis with epididymis. Histopathological examination included brain, thoracic spinal cord, pituitary, thyroid, adrenal, heart, lung, spleen, liver, kidney, stomach, small and large intestines, pancreas, ovary, uterus, prostate, salivary gland, mesenteric lymph nodes, urinary bladder, gallbladder, nerve with muscle, eye, bone marrow, and rib junction.

Except for signs of possible mild hepatic involvement, examination of clinical parameters, behaviour, body weight changes, organ weights, gross and microscopic pathology as well as ophthalmoscopic findings gave no indication of compound-related systemic toxicity. All dogs showed slight to moderate body weight gains and food consumption was generally comparable between test and control animals. After 4 weeks, serum glutamic-oxaloacetic transaminase (SGOT) values were significantly higher in the exposed males in comparison with controls, but the SGOT values had returned to normal after 13 weeks. At 13 weeks there was indication of an elevation of this biomarker in the intermediate and high dose females. There were no significant effects on alkaline phosphatase, or on the serum glutamic pyruvic transaminase (SGPT) values in any of the exposed groups. Interpretation of the SGOT data is hampered by the low number of animals in each group, as well as by the significant drift in base-line values found in the control group at the start of the study, after 4, and 13 weeks respectively. In males, but not in females, there was a dose related trend for increase in absolute liver and spleen weights, but no significant differences in comparison with controls for organ weight/body weight ratios could be noted. All other organ weights and organ/body weight ratios were within historical laboratory limits and comparable to control values. Gross and microscopic pathology did not reveal any organ or tissue alterations that could be attributed to the administration of the test material. Although the report states that “All animals were observed daily for appearance, behaviour, appetite, elimination, and signs of toxic or pharmacological effects”, the study failed to identify neurotoxic effects of piperazine in the dog, although the highest dosage (145 mg/kg/day for 8 weeks) considerably exceeded the dose, as well as the time of administration that have been described in the veterinary literature, reviewed by Lovell (1990), to induce serious signs of neurotoxicity in dogs such as ataxia, muscular weakness, head pressing, hyperesthesia, and an unusual myoclonus (head and neck stretched out, front legs pulled back along the chest wall, and hind legs stretched outwards and back). Based on this study, the dose 50 mg/kg/day (equivalent to 25 mg/kg/day of piperazine base) was considered as a NOAEL in dogs by the EU Committee for Veterinary Medicinal Products (CVMP, 1999). For liver toxicity, a NOAEL of 25 mg/kg/day of piperazine base is proposed.

Supporting studies

Dow Chemical Co. (Lockwood, 1957) conducted a 90-day repeated dietary feeding study in groups of 10 male and 10 female rats per sex and dose at 1,000, 3,000, and 10,000 ppm anhydrous piperazine in the diet (corresponding approximately to 50, 150, and 500 mg/kg/day[5)] piperazine base), or 1,830, 5,500, or 18,300 ppm piperazine dihydrochloride in the diet (corresponding approximately to 45, 140 and 450 mg/kg/day piperazine base). Lungs, heart, liver, kidney, spleen and testes were removed upon sacrifice and processed for histopathological examination. No adverse effects were noted at 1,000 ppm; whereas degenerative changes of the liver with diffuse cloudy swelling and focal necrosis as well as fibrotic and degenerative changes were seen in the kidneys were reported at 10,000 ppm (500 mg/kg/day). At 3,000 ppm (150 mg/kg/day) these pathological changes were "somewhat milder". At the highest dose level there was a depression of weight increase that was statistically significant only for females. The study indicates a NOAEL of 50 mg/kg/day. With piperazine dihydrochloride no adverse effects were noted up to 18,300 ppm in the diet (450 mg/kg/day piperazine base), a finding that is difficult to explain and which raises serious doubts as to the validity of this study.

A low subchronic toxicity was also found in a more recent dietary two generation study in rats (see below) where a LOAEL of 12,000 (300 mg/kg/day), and a NOAEL of 5,000 ppm (125 mg/kg/day piperazine base) in the feed was found for F_0 males dosed for 10 weeks, and F_1 females for 11 weeks (Wood and Brooks, 1994). However, neither biochemical data, nor histopathology for other organs than the sex organs and accessory glands were undertaken that would permit an adequate assessment of a NOAEL for repeated dose exposure.

In a developmental toxicity study in rats (Ridgway, 1987b), pregnant rats were gavaged 0, 105, 420, or 2,100 mg/kg/day piperazine base during days 6-15. A NOAEL of 420 mg/kg/day was reported for the females based on excessive salivation, lethargy and a reduction in bodyweight gain, body weight, as well as food consumption in females of the top dose.

In a developmental toxicity study in rabbits (Ridgway, 1987b), pregnant rabbits were gavaged 0, 42, 94, or 210 mg/kg/day piperazine base during days 6-18. A NOAEL of 42 mg/kg/day was reported for the females based on decreased food consumption (-39%) and body weight gain during the 4 first days of dosing.

The administration of 110 mg piperazine (as the adipate) per kg body weight orally to rats for 8 weeks did not result in any significant pathological changes (Cross et al., 1954). Dow Chemical reports (cited in Trochimowicz et al., 1994), that inhalation of 100 ppm by guinea pigs for 3 hours, with 7 exposures during a period of 11 days failed to elicit any toxicological reactions.

A 30-day gavage study in rats performed at the University of Kerala, India, employing a dose of 150 mg/kg/day of piperazine hexahydrate (Kaleysa Raj, 1973) indicated "no untoward visible symptoms". Apart from the lipid content of selected tissues and blood glucose levels, data that permit evaluation of this study published as a "short communication" are entirely lacking.

There are some indications that piperazine modulates the lipid metabolism in rodents. Thus, per oral administration of 70 mg/kg/day for 30 days was reported to reduce the levels of

[5] rat food factor, 1 ppm in feed, 0.05 mg/kg/day

serum lipids in rats (Raj, 1973), and in rabbit males raised on a cholesterol rich diet a high dose of piperazine given during 5-10 weeks reduced the levels of cholesterol in blood, aorta and liver. The results are difficult to interpret, because it was reported that the effect in female rabbits was the opposite, i.e. piperazine increased the cholesterol levels. No effect was noted on the levels of triglycerides, nor had piperazine any effect on the lipids in male rats fed a cholesterol deficient diet (Redgrave and West, 1972). The authors advance the hypothesis that the observed differential effect could be due to formation of stable estrogen-piperazine complexes *in vivo* (Beall et al., 1953) that could modulate the hormonal control of cholesterol metabolism.

Data gaps (neurotoxicity)

Piperazine has been extensively used as an anthelmintic for veterinary uses, where the recommended doses (piperazine base) is 110 mg/kg for swine, cattle and horses, and 45-65 mg/kg for dogs and cats (Lovell, 1990). Neurological side effects upon the oral administration of piperazine salts as anthelmintic have been described in dogs (Sloan et al., 1954; Bownass, 1987; Wooliscroft, 1987), cats (Stoffman and Braithwaite, 1976; Swift, 1984; Goodard and Johnston, 1986), the puma (Rettig, 1981), tigers, lions (Christoph et al., 1962), horses (Drudge et al., 1974; McNeil and Smyth, 1978), as well as in sea lions (Gray, 1972). The tigers and lions that exhibited neurological symptoms were administered a single dose of about 300 mg piperazine citrate per kg bw (Christoph et al., 1962). In dogs, typical symptoms are acute distress, ataxia, with head and neck stretched out, front legs pulled back along the chest wall and hind legs stretched outwards and back. In cats, tigers and lions, lethargy, and tonic seizures as well as marked lack of muscular coordination with ataxia have been described. Such reactions have been noted after single (usually, but not always an overdose), as well as upon multiple treatments, where felidae species seems to be particularly sensitive.

The rabbit appears also to be sensitive, in as much as some of the effects described above were observed after oral administration of 210 mg/kg/day piperazine base for 12 days to pregnant animals during a teratological study (Ridgway, 1987b).

Further, in a preliminary study in rabbits, changes in the EEG pattern were reported upon the administration of daily doses of an unspecified salt of piperazine at 150 mg/kg by gavage for four days or at 200 or 250 mg/kg for 1-2 days (Kuelz and Rohmann, 1969). These observations provide experimental support for the clinically observed neurotoxic effects in humans and animals at high doses (See Section. 4.1.2.6.2.). The EEG-changes in rabbits were reported to be abolished by the simultaneous injection of vitamin B_6.

The observation that intraperitoneal injection of a single dose of about 200 mg of piperazine base given to the guinea pig as the tripiperazine dicitrate caused death in tetanic convulsive seizures (Ratner et al., 1955), also deserves mentioning in this context in view of the fact that similar reactions are elicited by piperazine in felidae species (Rettig, 1981), as well as the lowered seizure threshold in human epileptics (see below).

There were no apparent neurotoxic effects in the 2-generation study in rats cited below (highest dose 625 mg/kg/day) (Wood and Brooks, 1994), although neurotoxic effects, evidently mainly of cholinergic nature (excessive salivation) was noted at 2,100 mg/kg piperazine base given orally to rats in a teratology study (Ridgway, 1987b).

The mechanisms of neurotoxicity induced in mammals has not been elucidated, but in rat phrenic nerve-diaphragm preparations, piperazine citrate was shown to possess neuromuscular blocking activity, and at high doses (corresponding to 70 or 140 mg/kg

piperazine base) decreased the threshold for convulsions induced by leptazol or strychnine in mice (Onuaguluchi and Mezue, 1987). A number of investigations on the mode of action of piperazine in *Ascaris* have been conducted. In contrast to compounds like eserine and diethylcarbamazine, piperazine had no potentional action on the effects induced by acetylcholine in nerve-muscle preparations from *Ascaris suum* (Natarajan et al., 1973). It has, on the other hand, been demonstrated that piperazine acts as a gamma-amino butyric acid (GABA) agonist in this species. In the somatic muscle cells of this parasitic nematode, GABA receptors are present that gate chloride conductance in a similar fashion to the mammalian GABAa receptor subtype. The receptors are similar, but not identical to those of the mammalian host. The most potent GABAa agonists are also potent in *Ascaris*, but the effect of muscimol is less than for the vertebrate receptor, and the *Ascaris* receptor is also not as sensitive to antagonists such as picrotoxin. In this invertebrate the effect on the somatic muscle GABA receptors results in interference with neuromuscular transmission causing a reversible paralysis (Martin, 1993; Martin et al., 1996). In mammals, motorcortical GABAa inhibition is important for initiation of smooth flexion and/or extension movements of the extremities affecting motor and postural control. When injected into the hand motor cortical area of three infant macaque monkeys, the GABA agonist muscimol disrupted forelimb movement showing a posture of dropped wrist and fingers as if the radial nerve were paralysed. Interestingly, the three investigated animals exhibited large inter-individual differences in sensitivity to the action of the same dose of muscimol, being low in one, moderate in the second and substantial in the third (Kubota, 1996). Injection into the medial segment of globus pallidus elicited choreiform movements and injections into substantia nigra pars reticulata provoked severe axial posture anomalies with rotational behaviour as well as contralateral hypotonia (Burbaud et al., 1998). Although the symptoms induced by piperazine in sensitive species exhibits some of these features, it is possible that its effects in mammals also involve other modes of action as well, in as much as a nicotinic action on rat sympathetic ganglia *in vitro* was reported in one series of experiments (Connor et al., 1981).

Summary

Upon repeated dose oral administration to rats and dogs, except for some signs of liver toxicity, little evidence of systemic toxicity was observed even at the highest tested dose. A NOAEL of 25 mg/kg/day of piperazine base for induction of mild hepatic involvement in the Beagle dog can be established. Although inadequately reported, a 90 day study in rats indicates an approximate LOAEL of 150 mg/kg/day based on histopathological changes in liver and kidneys. A few oral doses ranging from about 50 to 300 mg/kg piperazine have been found to elicit signs of serious neurotoxicity in domestic dogs and cats, horses, sea lions, pumas, lions, as well as in tigers. The mechanism of the neurotoxicity induced by piperazine in mammals is unknown, although it may be assumed that similarly to its action in invertebrates, it acts as a GABA agonist. The inability to detect any signs of such toxicity in available subacute and subchronic studies is a reason for concern, and makes it impossible to establish a LOEL or NOEL with respect to this important toxicological endpoint. It is established beyond doubt that piperazine after 1-7 administrations induces neurotoxicity in some mammalian species including humans, where children appear to be particularly sensitive. It is, therefore, considered that this end-point has not been adequately investigated.

4.1.2.6.2 Studies in humans

Although neurotoxic side effects were reported at the end of last century when piperazine was used at doses of (>10 g; corresponding to doses >144 mg/kg if assuming a body weight of

70 kg) for the treatment of gout (Stewart, 1894; Slaughter, 1896), the various salts of piperazine that have been extensively used as anthelmintic drugs since the beginning of the 1950s. In general, it demonstrated a low order of toxicity when used in the recommended dose of 100 mg/kg for adults and 50-65 mg/kg in children for up to 7 days (White and Standen, 1953). However, reversible neurotoxic effects including muscular weakness, unsteadiness, lack of co-ordination, hypotonia, diminished tendon reflexes, but also tremor, clonic spasms, dysarthria, diffuse EEG disturbances, mental confusion and hallucinations have been observed.

The fact that piperazine is able to induce neurotoxicity subsequent to the administration of a few daily doses is supported by numerous case reports from Europe, USA, the Middle East and South-East Asia. For this reason the registration of this substance as a pharmaceutical speciality has been withdrawn by the competent authority in Sweden as well as in some other countries. It has not been possible to reproduce this kind of toxicity in rats or mice, whereas there is solid support for piperazine-induced neurotoxicity in several other mammalian species. For determination of a LOAEL for this toxicity endpoint, the clinical reports dealing with neurological findings - including abnormal effects on EEG - in adults and children in absence of over dosage or previous relevant serious disease, like renal impairment and epilepsy, are of paramount importance. Several studies fulfilling this criterion have been located in the literature where the dosages as well as other parameters were relatively well defined, and they will be described in more detail below:

Most important studies

Belloni and Rizzoni (1967), Paediatric Clinic, University of Pavia, Italy. After treatment of a four-year-old child for 3 days with 100 mg/kg bw piperazine hexahydrate (44 mg/kg b.w. piperazine base), severe asthenia, tottering gait, poor balance, extreme muscular weakness, and EEG changes developed. This first case caused the clinic to investigate all children under treatment with piperazine. In 10 out of 11 children treated with piperazine (hexa) hydrate 80 mg/kg bw (35 mg/kg bw piperazine base) per day for five days, abnormal EEG changes were noted that were similar to those previously described in the literature (i.e. continuous bilateral spikes and polyspikes and high-voltage waves interspaced with slow-wave activity). Only one of the children was reported to suffer from clinical abnormality that could cause confounding (enlarged liver due to chronic cardiac failure). Upon repeated treatment, after normalisation of the EEG, of 6 of the children with piperazine hydrate at the same dose together with 1 mg/kg bw prednisone per daythe EEG changes either did not appear, or were reported to be less pronounced.

Padelt and coworkers (Padelt et al., 1966), Kinderklinik des Städtischen Klinikums Berlin-Buch und Institut fuer Kortiko-Viszerale Pathologie und Therapie der Deutschen Akademie der Wissenschaften zu Berlin-Buch, Germany. Of all reports in the literature, this study covers the largest patient material on induction of EEG abnormalities by piperazine in children. The cohort consisted of 89 children, 41 boys and 48 girls, who had been hospitalised mostly for infectious diseases, and where pinworm infection later had also been diagnosed. Treatment with piperazine took place about 10 days after the symptoms of the main acute illness had subsided. Children showing deviating EEG-pattern were excluded from the study. The study was designed to specifically look for signs of neurotoxicity of a ‘one day’ dose (see below). The dose was somewhat higher than subsequently became therapeutically recommended. The children were studied by EEG the day before treatment and the day after treatment. Piperazine hydrate (hexahydrate) was administered twice (12 hours apart) during one day at the following total doses: 3 g at the age of 1-2 years, 5 g up to 5 years, 6 g up to 7

years, 8 g up to 9 years, 10 g up to 11 years, and 12 g at the age of 12 years or older. However, most children were 1-3 years of age. Expressed as piperazine base, the authors report that the dose corresponds to a total 'daily' dose of 90-130 mg/kg. Considering the uncertainty in the dosing, the dosing interval will be interpreted as a dose of 110 mg/kg. No visible signs of neurotoxicity were observed.

According to increasing abnormality of the EEG patterns, the subjects were classified in 4 different groups:

Categorisation of effect	Number of children /group[a]	Number of children /category
Category A – No or light abnormalities		56
1) Normal EEG with respect to age.	16	
2) Light to moderate general changes.	40	
Category B – Moderate to severe changes		33
3) Increased activity with high amplitude waves and seizure potential.	11	
4) Tendency for a slow-down activity mostly occipital; many, mostly polymorphic theta waves or delta-frequencies (according to age). Occurrence of high amplitudes, often rhythmic slow waves, maximal occipital, multiple generalisations.	17	

a) 5 children in Category B were not assigned any group, as the effects were intermediate to those in groups 2 and 3.

In 56 children (63%) the EEG changes could be classified into Category A (no or light effects), and in 33 (37%) in Category B. However, 5 cases in the latter group were placed in between group 2 and 3, making the table above somewhat unclear.

No association between abnormal EEG pattern and infectious disease or with age could be noted. Category A contained 5 cases of encephalitis and 1 with meningitis (out of 56), whereas in Category B, there were 1 case of encephalitis and 3 with meningitis out of 33 cases.

Main supporting documentation

Berger and co-workers (Berger et al., 1979), Department of Neurology, Hadassah University Hospital, Jerusalem, Israel, reported neurotoxic effects (bilaterally symmetric hypotonia, dysdiadochokinesis, and dysmetria with past pointing and a considerably ataxic gait) in a previously healthy 33-year old woman who had taken 11 mg piperazine adipate per kg bw four times a day (i.e., 44 mg/kg/day) for seven days (corresponding to 16 mg/kg bw per day as piperazine base). After discontinuation of therapy, the patient's condition improved, and clinical examination, including blood chemistry, BUN and liver enzymes and urinalysis gave normal values.

Bomb and Bedi (1976), Department of Medicine, R.N.T. Medical College, Udaipur, India. A 12-year-old girl was given a single dose of 100 mg/kg bw piperazine citrate (tripiperazine dicitrate; corresponding to 24 mg/kg bw per day of piperazine base) at bedtime for ascariasis.

Next morning she was unable to sit up in bed without support. Neurological examination revealed horizontal nystagmus, generalised diminution of muscle power (she was quite unable to stand or sit without support), hypotonia and diminished tendon reflexes. After 24 hours the symptoms had disappeared. There was no previous history suggestive of any neurological, renal or hepatic disease, and her blood urea values were found to be normal.

Conners (1995) Emergency Medical Trauma Centre, Children's National Medical Centre, Washington, D.C., USA, reports a case of a previously healthy nine-year-old boy who was transferred to the emergency department because of incoordination, frequent falling, and repeated dropping of objects. He had been administered piperazine citrate at a dose of 65 mg/kg (23 mg/kg bw) each morning for seven days. The patient's gait was broad based, and his finger-to-nose and heel-to-shin tests were markedly abnormal. Rapidly alternating movements were poorly performed. No other physical abnormalities could be detected, and after 24 hours the symptoms were resolved.

Drouet and Valance (1994), Service de Neurology, Hopital d´Instruction des Armées, Saint-Anne, Toulon Naval, France. A 50 year-old woman weighing 65 kg, and who had been administered piperazine at a dose corresponding to 30.5 mg/kg piperazine base for five days, developed myoclonus that increased in intensity, while on the 5th day, a transitory diplopia, and difficulty in walking arose which precipitated hospitalisation.

Clinical examination revealed myoclonic contractions that were enhanced by active muscular movements. These were uni- or bilateral, preferentially of the extremities, but also with respect to the cervical area. The patient exhibited ataxic gait, and abnormal EEG, but no other clinical abnormalities that suggested an underlying disease. The only deviating finding was a mild microcytic anemia and a moderate eosinophilia that would have had no impact with respect to the observed neurotoxic effects. All symptoms disappeared gradually after 4 days post piperazine treatment.

Eliachar and coworkers (Eliachar et al., 1960). Hopital d´Aulnay, France, describe the intoxication of a child aged 2 years and 9 months who was treated for 5 days with one daily teaspoon of piperazine syrup, corresponding to about 100 mg/kg bw piperazine (hexa) hydrate per day (44 mg/kg bw piperazine base per day). The child was unable to sit upright and exhibited uncoordinated movements and a marked hypotonia upon clinical examination. No other abnormalities could be detected. Three days after hospitalisation, EEG was performed, and the abnormal wave patterns indicated a diffuse cerebral involvement. Three days later the EEG had returned to almost normal.

Ljunggren (1967), the Academic Hospital, Uppsala, Sweden. A 3 and-a-half-year old, previously healthy girl who had received 5 daily consecutive piperazine doses corresponding to 50 mg/kg bw piperazine base per day developed neurological signs, where after treatment was interrupted. 4 days later, when the symptoms had disappeared, treatment was reinstituted at the same dosage level, and the neurological symptoms appeared again, which precipitated hospitalisation. Clinical examination revealed ataxia and inability to stand upright, but no obvious loss of muscle tone. EEG examination performed 36 hours after hospitalisation gave evidence of "a rather severe pathological activity of unspecific as well as paroxysmal nature especially covering postcentral regions". Gross clinical neurological symptoms subsided within 2 days, but although there was certain normalisation, still after two weeks an abnormal EEG pattern persisted. However, although the remaining abnormalities may here have been obscured by a possible secondary adenovirus infection, the findings were highly consistent with those reported in the literature.

Several other case reports of varying quality and size do also exist (Bettecken, 1956; Combes et al., 1956; Wechselberg, 1956; Cavalcante and de Mello, 1958; Schuch et al., 1963; Külz, 1964; Fassetta, 1965; Point, 1965; Neff, 1966; Chateau et al., 1966; Savage, 1967; Külz and Rohmann, 1967, 1969; Miller and Carpenter, 1967; Sethi et al., 1968; Jakubowska et al., 1968; Boulos and Davis, 1969; Parsons, 1971; Fournier et al., 1972; Kömpf and Neundörfer, 1974; Vanneste et al., 1975; Gupta, 1976; Graf, 1978; Solanki, 1978; Sörensen, 1980; Lahori and Sharma, 1981; Neau et al., 1984; Yohai and Barnett, 1989; Buemi et al., 1995; Nickey, 1996).

Conclusion: This section deals with clinical observations in human patients where the evidence obviously have to be assessed in a manner different than is e.g. the case for data from controlled animal studies. As for all clinical studies of similar nature, the above-cited reports - each of them taken singularly – naturally, have certain weaknesses. However, taken together they, nevertheless, offer convincing evidence for piperazine neurotoxicity at recommended doses without predisposing factors present. It is not possible to single out one particular "key study", as is commonly done for animal testing. Nevertheless, taken for granted that the physicians involved, many of whom were associated with well-known clinics, had sufficient competence to adequately characterise the clinical findings, special weight must be given to the report from Belloni and Rizzoni (1967) as well as the one published by Padelt et al. (1966) in children, because the dose schedules were clinically supervised, and the material relatively large. The fact that only a minority of all patients developed neurotoxicity, cannot be cited as evidence against a causal association, but rather reflects large differences in individual sensitivity, a well-known observation that must be taken into consideration.

As described under Section 4.1.2.6.1 above, piperazine has been demonstrated to be a GABA agonist in *Ascaris*, and many of the symptoms elicited in some humans resemble those caused by the potent GABA agonist muscimol. The large inter-individual differences in sensitivity to a GABA agonists like muscimol found in the sub-human primate (Kubota, 1996) and that were described above, may here be highly relevant.

Piperazine has been reported to induce hemolytic anaemia in an individual deficient in glucose-6-phosphate dehydrogenase (Buchanan, 1971). However, no conclusions can be based on this singular finding.

Besides asthma, chronic exposure to piperazine has been found to induce chronic bronchitis. The over-all prevalence of bronchitis among the Swedish workers involved in piperazine production and processing was found to be around 16%, exhibiting a clear dose-response relationship (Hagmar et al., 1984).

Occupational exposure to sensitising compounds like isocyanates have been reported to induce a syndrome described as "small airways disease", implying obstruction of peripheral airways smaller than 2 mm in internal diameter (Hjortsberg et al., 1983). Such obstruction may not always be detected by conventional tests such as spirometry, but can be diagnosed by nitrogen-wash-out techniques, whereby the volume of trapped gas in the lungs can be measured. However, in the Swedish workers exposed to piperazine, no such effects could be detected (Hagmar et al., 1987).

4.1.2.6.3 Summary of repeated exposure

A NOAEL of 25 mg/kg/day of piperazine base for liver toxicity in the Beagle dog can be established. This NOAEL was chosen by EMEA (The European Agency for the Evaluation of

Medical products) as the basis for setting an ADI and provisional MRLs for the use of piperazine as a veterinary anthelmintic in pigs and poultry (EMEA, 2001a).

However, adequate chronic bioassays are not available, and the fact that none of the systematic experimental studies reported neurotoxic effects is a cause for serious concern. Such effects, that occasionally are serious, have been well documented in clinical practice, and have also been described by veterinarians in rabbits, dogs, cats, tigers, horses, the puma, and sea lions. For previously healthy humans, a LOAEL of about 30 mg piperazine base/kg/day can be established for a limited 3-7 day's treatment period. Since there is little information on effects at lower doses than the therapeutic dose, the 30 mg/kg/day dose should rather be regarded as a 'low OAEL' than a true LOAEL. Although this dose will still be called the LOAEL (instead of introducing new terms), the observation that this is not a true LOAEL should be kept in mind when discussing the MOS. Based on existing data, a NOAEL cannot be established for neurotoxicity induced by piperazine, either in a sensitive animal species or in humans upon long-term exposure. The LOAEL of 30 mg/kg/day for a limited 3-7 days exposure of humans will be used in the risk characterisation. The human neurotoxicity data has been given preference over the dog-based NOAEL cited above. The reasons are the higher relevance of studies in humans (e.g., as regards human sensitivity to the toxic effect) as compared to animal data, and the lower need for assessment factors when basing the risk characterisation on studies in humans as compared to studies in animals. As such, neurotoxicity could also be considered of higher concern than mild hepatic effects.

In humans, repeated exposure to piperazine by inhalation may induce chronic bronchitis, but no LOAEL or NOAEL can be established for this endpoint.

4.1.2.7 Mutagenicity

4.1.2.7.1 *In vitro* studies

Using the strains TA 1535, TA 1537, TA 98, and TA 100, piperazine tested at the concentrations 33, 100, 333, 1,000, or 2,167 μg/plate was found to be negative in the *Salmonella typhimurium* reverse mutation test with and without metabolic activation (Haworth et al., 1983).

In a study with piperazine phosphate conducted in accordance with OECD test guideline requirements these results could be confirmed (Marshall, 1986) using strains TA97 and TA98 (frameshift mutations) as well as with TA 100 and TA1535 (base-pair substitution) with concentrations ranging from 8-5,000 μg/plate.

Neither the citrate, adipate, mebendazole or thiabendazole salts of piperazine were found to induce reverse mutations, mitotic recombination, or gene conversion in *Saccharomyces cervisiae* (Hennig et al., 1987).

At concentrations ranging from 1.7 to 110 mg/ml, piperazine phosphate was also found to lack clastogenic properties in cultivated Chinese hamster ovary cells in presence and absence of metabolic activation in a GLP study (Allen et al., 1986).

Conaway et al. (1982) reported, that piperazine induced mutations in the L5178 mouse lymphoma test upon metabolic activation in a poorly documented study.

However, in another mouse lymphoma test using test solutions containing 200, 250, 300, 350, and 400 µg/L of piperazine phosphate, negative results were reported both with and without metabolic activation (Cole and Arlett, 1976). A weak activity with respect to the induction of 6-thioguanine resistance was subsequently found in the presence of rat-liver microsomes in an adequately reported guideline mouse lymphoma fluctuation assay conducted according to GLP and using piperazine phosphate at a concentration of 400 µg/L, but these increases were within the historical solvent control range, and lacked reproducibility (Kennelly, 1987).

4.1.2.7.2 *In vivo* tests

Upon dosing groups of CD-1 mice orally with 5,000 mg piperazine phosphate per kg, no significant increase in the level of micronuclei of polychromatic or normochromatic erythrocytes of the bone marrow could be detected in an adequately performed GLP study (Marshall, 1987). In an initial toxicity range-finder study, two male and 2 female mice each received the test article orally at a dose of 4,000, 4,500 and 5,000 mg/kg. No lethality was observed at 5,000 mg/kg, a dose that was subsequently utilised in this micronucleus test.

Carboxymethyl cellulose in distilled water served as negative control. Cyclophosphamide (CPA), dissolved in water and administered orally at 80 mg/kg to one group of 5 male and 5 female mice which were killed after 48 hours provided the positive control. Groups of 5 male and 5 female mice treated at 5,000 mg/kg piperazine were sacrificed and sampled after 24, 48 and 72 hours. In general, positive control animals exhibited toxicity in the bone marrow as seen by an increased proportion of normochromatic erythrocytes (NCE), and increased numbers of micronucleated polychromatic erythrocytes (PCE) and NCE such that the micronucleus frequency in the positive control group was significantly greater than in controls ($p < 0.001$).

Negative control mice exhibited normal ratios of PCE to NCE with group means for males and females ranging from 0.9 to 1.59, and normal frequencies of micronucleated PCE (mean 1.2-2.8/1,000) and NCE (range 0.32-1.8/1,000). Mice treated with piperazine phosphate exhibited ratios of PCE to NCE and frequencies of micronucleated PCE and NCE which were similar to controls. Group mean PCE/NCE ratios ranged from 1.16 to 2.04; mean frequencies of micronucleated PCE were 0.8-2.8 per 1,000 and of micronucleated NCE, 0.9-2.85. No statistically significant treatment-related increase in micronucleus frequency was found in any of the animals receiving piperazine phosphate at any sampling time.

Wistar rats were partially hepatectomized and the liver labeled during regeneration using tritiated tymidine. After 2 weeks a single dose of 50 mg piperazine, 10-50 mg/kg N,N-dinitrosopiperazine were administered by i.p. injection. Liver DNA was isolated and single and double strand breaks deteermined by the alkaline elution technique. Whereas the dinitrosopiperazine gave positive results, there was no indication of any DNA damage induced by piperazine as such (Stewart and Farber, 1973). Likewise, piperazine alone was without effect in the host-mediated *S. typhimurium* (TA 1950) mouse assay (Braun et al., 1977).

N-mononitrosopiperazine (NPZ) as well as N,N'-dinitrosopiperazine (DNPZ) have been found to induce mutations *in vivo* in the host-mediated *Salmonella typhimurium* mouse assay (Zeiger et al., 1972). Further, using this assay a positive response was also obtained upon co-administration of piperazine dihydrochloride and nitrite (Braun et al., 1977).

4.1.2.7.3 Human genotoxicity

30 male Swedish workers exposed to piperazine and 30 controls were investigated with respect to induction of micronuclei in peripheral lymphocytes (Högstedt et al., 1988). An increased incidence of non-Hodgkin's lymphoma had previously been reported for this cohort of workers (Hagmar et al., 1986). There was a significant increase in the frequency of micronuclei in cultured lymphocytes when cell division was stimulated with pokeweed mitogen, but not when phytohemagglutinin was used. This can be explained by the fact that the two different mitogens stimulate different subpopulations of lymphocytes with differential sensitivity towards clastogens. Thus, phytohemagglutinin mainly stimulates T-lymphocytes and pokeweed mitogen is specific for B-lymphocytes. Although statistically significant, the increase was modest (1.1 versus. 0.6%), and 4 of the exposed and two of the controls were outliers exhibiting much higher incidences (3% versus 2%). Whereas the incidence of micronuclei was increased when using pokeweed mitogen as compared to phytohemagglutinin, this was not the case for lymphocytes derived from controls. However, the interpretation of the results from this study is uncertain, in as much as many other organic chemicals were manufactured in the same plant, including genotoxic agents such as ethylene oxide, from which it is synthesised. No information on more recent exposures to these other chemicals that could result in significant confounding is provided in the report.

A number of parameters that were claimed to be associated with the induction and repair of DNA damage were studied for the same cohort as described above (Pero et al., 1988). The studied parameters included unscheduled DNA synthesis (UDS) upon induction by N-acetoxy-N-acetyl-2-aminofluorene (NA-AAF), constitutive and gamma radiation induced adenosine diphosphate ribosyl transferase (ADPRT), epoxide hydrolase, and glutathione transferase in resting mononuclear leukocytes from 76 exposed workers. Epoxide hydrolase and glutathione transferase activity were unaffected. However, UDS induced by NA-AAF as well as ADPRT activities were significantly elevated as compared to a control group of 48 workers. However, the authors point out that potential exposure may have involved over 100 chemicals including many well-known carcinogens, and no apparent significant associations to a specific exposure could be established. Further, epoxide hydrolase as well as glutathione transferase are not involved in either the direct generation, or repair of DNA damage, and the utility of the other two markers for detecting DNA damage present in the lymphocytes prior to challenge by ionising radiation and N-acetoxy-N-acetyl-2-aminofluorene can also be questioned.

4.1.2.7.4 Summary of genotoxicity

Studies conducted *in vitro,* as well as *in vivo* indicate that piperazine does not induce point mutations or chromosome aberrations. Due to the likelihood of exposure to other clastogenic chemicals, the significance of the modest increase in micronuclei seen in one cohort of exposed workers cannot be ascertained. However, nitroso-piperazines that can be formed by nitrosation of piperazine *in vivo* demonstrate clear genotoxic properties (*in vivo* DNA strand breaks and mutations).

4.1.2.8 Carcinogenicity

4.1.2.8.1 Studies in animals

Groups of 15 MRC rats per sex were given 0.025% of piperazine in the drinking water (20-25 mg/kg/day), 5 days/week, during 75 weeks after which the animals were kept until death and subjected to complete pathological examination. The dosed animals did not exhibit any increase of tumours in comparison with 15 male and 15 female controls (Garcia and Lijinsky, 1973).

When administered at 6.25 g/kg in the feed (about 938 mg/kg/day[6]) for 28 weeks and sacrificed at 40 weeks, it failed to induce any significant increase in the incidence of lung adenomas in groups of 40 Swiss mice per sex in comparison with controls (80 animals per sex) (Greenblatt et al., 1971). It is not possible to judge the extent of histopathological examination performed upon autopsy, but in addition to lung adenomas, lymphomas, liver, mammary glands, as well as sex organs seem to have undergone examination. The only significant finding was a reduction in the number of malignant lymphomas in the piperazine treated animals.

Similar treatment of strain A mice with piperazine at 6.3 (938 mg/kg/day), or 18.8 g/kg (2,820 mg/kg/day) for 25 weeks, followed by a 13 weeks follow up post dosing, did not significantly increase the number of animals with lung adenomas. No histopathological analysis of other organs seems to have been performed (Greenblatt and Mirvish, 1973).

Available carcinogenicity studies with piperazine are scantily reported and do not meet present days' standards in most respects.

N-mononitrosopiperazine (NPZ) as well as N,N'-dinitrosopiperazine (DNPZ) have both been found to be carcinogenic in rodents, out of which the latter compound is the more potent (Druckrey et al., 1967; Garcia et al., 1970; Love and Lijinski, 1977). In two of these studies, NPZ was administered at different dose levels in drinking water. In the study conducted by Love and Lijinski (Love and Lijinski, 1977), where MRC-rats were administered NPZ at 400 and 800 mg/L in the drinking water, corresponding to a daily average dose of about 27 and 54 mg/kg, a clear dose response relationship was found with respect to the induction of tumours in the nasal cavity.

With the exception for a non-significant increase in pituitary adenomas in females treated with a combination of piperazine and nitrite (6/12 versus. 3/13 in controls), there was no increase in tumour incidence in groups of 15 MRC rats per sex were given 0.025% of piperazine plus 0.05% sodium nitrate in the drinking water (20-25 mg/kg/day), 5 days/week, during 75 weeks (Garcia and Lijinsky, 1973). However, adenoma of the pituitary is one of the most common neoplasms in the rat, and the observed increase lies within the historical control incidence for such old (100 weeks) animals of this strain. None of the types of tumours typical of nitrosamines, e.g. of the nasal cavities, exhibited any increase.

Swiss mice administered piperazine at 6.25 g/kg in the feed (about 938 mg/kg/day) together with 1 g nitrite per L of drinking water, 5 days per week for 28 weeks with sacrifice at 40 weeks (Greenblatt et al., 1971). A significant increase in lung adenomas (64% adenoma-

[6] mouse food factor; 1 ppm = 0.15 mg/kg/day

bearing mice versus. 14% in controls) was found in groups of 40 Swiss mice per sex in comparison with controls (80 animals per sex). There was no increase in any other type of tumours. Further, the data for the sexes were not reported separately, and it should be kept in mind that spontaneous incidences of lung adenomas up to about 50% in females have been reported for certain strains of Swiss mice (Sher, 1974).

In a subsequent study in strain A mice **(**Greenblatt and Mirvish, 1973), varying doses of piperazine were administered with the feed (104-2,820 mg/kg/day) together with a constant concentration of nitrite in drinking water (1 g/L) to groups of 40 animals per sex for 5 days per week during 25 weeks with sacrifice after another 13 weeks post dosing. In a second series in this study, various amounts of nitrite were given in drinking water (0.05-2.0 g/L), keeping the concentration of piperazine in food at a constant level of 938 mg/kg. Except for the combination 938 mg piperazine/kg feed, plus 0.05 g nitrate per L in drinking water, an elevation in lung adenomas was seen for all combined exposures. No data for other types of tumours were reported. However, the strain A mouse has long been known to be extraordinarily susceptible to induction of adenomas of the lung by a host of initiating as well as cancer promoting substances. As reported by many investigators, the spontaneous incidence of this tumour is high and, in addition, extremely variable. Thus, Heston (Heston, 1942) reported an incidence of pulmonary tumours in control A mice of 20% at 6 months of age, 50% at 12 months, and 90% at 18 months. Not only are these background rates affected by exposure to carcinogens, but also to a number of unspecific factors. Thus, diet restriction decreases the incidence, whereas corticosterone increases the incidence. Apart from the fact that the background incidence in controls was high also in this case, as well as it was strikingly variable (32% of control mice with adenomas in the first experiment, and 13% in the second), possibly indicating lack of randomisation of the animals with respect to the dosage groups. For the above-mentioned reasons, it is very difficult to draw any valid conclusions from these studies.

4.1.2.8.2 Human carcinogenicity

In a retrospective cohort study including 664 male workers employed in a Swedish chemical plant - where exposure to piperazine as well as to a number of other chemicals, including carcinogens like ethylene oxide, epichlorohydrin, and urethane had occurred - a statistically significant increase in cancer morbidity was observed for malignant lymphoma/myelomatosis. However, due to confounding by mixed exposures, it is not possible to draw any valid conclusions from this observation. A case-control study conducted within the cohort did not reveal any significant association with any specific chemical (Hagmar et al., 1986).

4.1.2.8.3 The Relevance of Secondary Nitrosation of Piperazine.

The formation of nitrosamines by nitrosation of secondary and tertiary amino compounds, and their presence in some foods and beverages, as well as their formation in the acid environment of the human stomach has been a matter of considerable concern (Magee, 1982; IARC, 1991), and in a few cases has it been possible to link human cancers to the exposure of N-nitrosamines. Such examples are provided by the induction of nasopharyngeal carcinoma in populations consuming Cantonese-style pickled fish containing high levels of dimethyl- as well as diethylnitrosamine (Fong, 1982). (Yu et al., 1986), as well as cancers of the oral cavity and pharynx caused by tobacco specific nitrosamines (IARC, 1985; Nilsson, 1998). The two nitrosated derivatives of piperazine, N-mononitrosopiperazine (NPZ) as well as

N,N'-dinitrosopiperazine (DNPZ) have been found to induce mutations *in vivo,* and have also been found to be carcinogenic in rodents (see Section 4.1.3.1.6).

In the assumption that N-mononitrosopiperazine is carcionogenic in humans the Committee for Veterinary Medicinal Products (EMEA, 1999) made calculations to quantify the possible carcinogenic risk of piperazine with the help of various mathematical models and with due attention to those reservations that exist in this context. The conclusion was that the calculations indicate that if there is any risk at all it seems to be extremely small for the populations for which the Committee made their assumptions.

4.1.2.8.4 Summary of carcinogenicity studies

Although there are no solid indications of a carcinogenic effect of piperazine, either in animal studies, or from the investigation in humans, the supporting database is insufficient to permit definite conclusions. However, in view of lack of genotoxic action, it appears unlikely that piperazine poses a carcinogenic risk. The two nitrosated derivatives of piperazine, NPZ and DNPZ, whereof the first has been identified as a minor metabolite of piperazine, have been found to induce mutations *in vivo,* and have also been found to be carcinogenic in rodents (see Section 4.1.3.1.6).

4.1.2.9 Toxicity for reproduction

4.1.2.9.1 Studies in animals

Developmental studies

Groups of 24 female Charles River CD(SD)BR rats were administered 250, 1,000, or 5,000 mg/kg bw of piperazine phosphate (corresponding to 105, 420 or 2,100 mg/kg piperazine base) by gavage during pregnancy days 6 to 15. Clinical signs, body weight and food consumption were recorded and the animals sacrificed at day 20 and the foetuses subjected to detailed external, visceral and skeletal examinations. Although there were no treatment-related deaths, signs of maternal toxicity were observed at the highest dose level, including excessive salivation, lethargy and a reduction in bodyweight gain (days 6-15), body weight (7% at day 15), as well as food consumption (14% during days 6-11 and 9% days 11-15). At this dosage, a lower foetal weight was also recorded (7%), but no evidence of teratogenicity was reported at any dose level. Pre- and post-implantation losses, litter size and sex rations were unaffected by piperazine treatment (Ridgway, 1987b).

A study performed according to GLP has also been performed to assess the effects of piperazine phosphate on the embryonic and foetal development in the New Zealand white rabbit (Ridgway, 1987a). The study does not fulfil the requirements of the present OECD Guideline 414, as the exposure period only covers the period of organogenesis. Groups of 16 animals were dosed by oral intubation of 0, 100, 225, and 500 mg piperazine phosphate per kg bw and day suspended in 1% w/v methyl cellulose. The doses correspond to 0, 42, 94, or 210 mg/kg piperazine base). The females were treated from days 6 to 18 of pregnancy, while registering clinical signs, bodyweights and food consumption. The dams were killed on day 28 of pregnancy and necropsy performed. The foetuses were subjected to detailed external, visceral and skeletal examination. At 210 mg/kg/day piperazine base overt signs of toxicity were observed in the treated dams including signs of neurotoxicity as demonstrated by excessive salivation and nervousness noted in all treated animals. Other symptoms of

adverse effects were anorexia, reduced or no faeces production, reduced food intake (e.g., by 85% days 6-14) coupled with body weight loss (high dose animals lost 9% of body weight whereas controls gained 6%). Two females were killed in extremis and one female aborted. The sacrificed females were found to have intestinal abnormalities including erosion of the mucosa of the stomach or duodenum. At 94 mg/kg/day piperazine base, there were no effects on body weight, although food consumption (-39%) and body weight gain were transiently reduced during the 4 first days of dosing. One female aborted, and five females were observed with reduced faeces production for short periods. One female died, but this was ascribed to accidental dosing into the lungs. No effects were observed at 42 mg/kg/day piperazine base. Although borderline, 94 mg/kg/day piperazine base may be considered to constitute the maternal LOAEL in this study.

At 210 mg/kg, piperazine base was highly embryotoxic and also demonstrated teratogenicity. Post-implantation loss was high with 100% resorptions in four litters. Foetal weights were reduced and there was a slight retardation of ossification. In addition, 15 of 56 (23%) foetuses (in a total of 8 litters produced) exhibited major abnormalities (6 cases of cleft palate and 9 cases of umbilical hernia) as compared with two of 86 (1.7%) in controls. The frequencies of major abnormalities in the four groups, expressed per litter, were 2/14, 4/14, 0/14, and 5/8 (with one additional case in an aborted high dose litter) in the control, low, mid, and high dose, respectively. Although specific and rare abnormalities, they have also been observed in food-deprivation studies in rabbits (Clarke, 1986). Thus, they can be considered to be secondary to the maternal toxicity. There was also an increased incidence of poorly ossified hindlimbs (epiphyses; 86% versus 40% variants in controls, and astragalus; 5.7% versus 0% of minor cases in controls) probably related to the maternal toxicity. At 94 as well as at 42 mg/kg piperazine base post-implantation loss, foetal weights, extent of ossification, and foetal sex ratios were unaffected by the treatment. Also, there was no significant increase in foetal abnormalities at the two lowest dose levels. Overall, the effects observed at 210 mg/kg/day piperazine base are considered to be secondary to maternal toxicity.

In summary, piperazine does not to appear to be teratogenic in the rat. In rabbits, such effects may be elicited at a dose level that is also toxic to the mother animal. The maternal LOAEL is 94 mg/kg/day, and the NOAEL 42 mg/kg/day piperazine base.

Multigeneration studies

In a two generation reproduction study in Sprague-Dawley CD rats performed according to OECD Test Guideline No. 416, groups of male and female animals were administered 0, 5,000, 12,000, or 25,000 ppm (250, 600, or 1,250 mg/kg/day) piperazine dihydrochloride in the diet throughout maturation, mating, gestation and lactation phases for two successive generations (Wood and Brooks, 1994). Expressed as piperazine base, the doses represent 125, 300, and 625 mg/kg/day. The F_0 males and females (32 per dose and sex) were dosed for 73 days for males and 17 days for females and paired within their respective dosage groups for up to 21 days. Subsequent exposure to diets continued throughout the breeding, gestation and lactation periods for both generations. At weaning of the offspring on day 21 *post partum*, 28 males and 28 females per dose group were selected at random to form the parental F_1 generation. The remaining generation was sacrificed and examined macroscopically. F_1 animals were given piperazine in the diet for 80 days, and all animals were observed for sexual development. Males and females were paired for up to 21 days and pregnant females allowed to deliver their offspring that were observed for growth and development. The adult F_0 animals as well as the F_1 males and females were sacrificed and examined macroscopically post mortem. Selected tissues and organs were weighed and/or retained in fixative. Selected

tissues and organs from the highest dose and control animals from F_0 as well as from F_1 adults were subjected to histopathological examination. In addition, in all F_1 females the implantation sites were counted. However, although macroscopic post mortem findings were recorded, the histopathological examination was limited to the sex organs and the pituitary. Parental animals were observed daily for clinical signs, and the body weights and food consumption recorded weekly during the maturation phase, which was continued for males after the mating phase. Mated females were weighted and food consumption recorded on specific days *post coitum* and *post partum*. The offspring were observed daily for clinical signs and the body weights recorded. During the lactation period the offspring were observed for intra-litter onset and duration of landmarks of physical development. On specific days of lactation, reflexological assessment of offspring was performed. These tests included investigation of the surface-righting reflex (day 1 *post partum*), mid-air righting reflex (day 17 *post partum*), startle reflex (day 21 *post partum*) and pupil reflex (day 21 *post partum*).

At the highest dose one F_0 female was found dead on day 19 *post partum*; no mortalities were seen at 300 or 125 mg/kg/day piperazine base. Also, no significant treatment related internal or external macroscopic lesions were noted in any of the dose groups, and no significant histopathological abnormalities could be detected microscopically in tissue sections from the reproductive organs from either males or females.

In **Table 4.16**, group mean bodyweights after 11 week's treatment are provided for F_0 and F_1 males as well as for F_0 and F_1 females before pairing. Also during gestation the body weight gain was reduced at the highest dose in F_0 (and 3% in mid dose animals at day 14) and from the middle dose in maternal F_1 animals. However, the corrected body weight gain (gain minus weight of uterus content) was not calculated. **Table 4.17** shows the group mean food consumption (fc) and food conversion ratios (fcr) before pairing at study week 10.

Table 4.16 Group mean body weights after 11 week's treatment for F_0 and F_1 males as well as for F_0 and F_1 females before pairing

Dose (mg/kg/day)	Generation	Bodyweight/Females	Bodyweight/Males
0	F0	273±15	569±58
125	F0	276±17	548±52
300	F0	273±13	534±43**
625	F0	265±12*	518±41***
0	F1	290±24	481±49
125	F1	291±26	470±52
300	F1	263±27***	440±54**
625	F1	240±22***	386±46***

Table 4.17 Group mean food consumption (fc) and group mean food conversion ratios[a] (fcr) before pairing at study week 11 for F1 males and females.

Dose (mg/kg)	fc, males F1	fc, females F1	fcr, males	fcr, females
0	29.5±3.0	22.0±1.0	0.09	0.04
125	29.3±1.5	22.0±0.8	0.09	0.05
300	28.7±1.3	20.6±1.0*	0.10	0.05
625	27.3±2.3	19.1±0.9***	0.11	0.06

* p<0.05
** p<0.01
*** p<0.001
a) Food conversion ratio = group mean body weight gain (g/day) during week divided by group mean food consumption (g/rat/day)

At 625 mg/kg/day piperazine base there was clear evidence of toxicity to the adult animals as judged by a statistically significant reduced body weight increase in both sexes for the F_0 as well as F_1 animals, an effect that was more pronounced in the second generation (F0 females, 3%; F_0 males 9%; F_1 females 17%, F_1 males 20%) (**Table 4.16**). Further, there was a reduction in number of pregnancies, reaching statistical significance only in F_1 (81.5% vs 100% in controls), and a reduced litter size at birth for both generations (59% and 32% of control values in F_1 and F_2, respectively) (**Table 4.18**), but no effects on live birth index, viability during lactation, or offspring physical development were noted when subjected to a set of reflexological tests. However, there was a delay in sexual maturation (appearance of vaginal opening for females and preputial separation for males) in both F_1 males and females (not investigated in F_2), but no significant differences in offspring sex ratios were noted at any dose level. However, it is likely that the delayed sexual observation could be related to the decreased body weights observed as from week 2 and onwards (roughly 25%, respectively), as shown in food restriction experiments by Carney et al (1998).

The reduced pregnancy index in combination with the decreased number of implantation sites and litter losses in F_2-adults indicate pre- as well as post-implantation losses.

Table 4.18 Summary of reproductive outcome

Generation	Endpoint	control	125 mg/kg/day	300 mg/kg/day	625 mg/kg/day
F0	number of animals paired	32	32	32	32
	numbers pregnant	29	29	32	21
	numbers with live offspring	29	29	32	21
	numbers failing to conceive	3	3	0	11
	number of females dying during lactation/parturition	2	0	0	1
	total litter loss	3	1	1	0
	number of implantation sites	n.i.	n.i.	n.i.	n.i.
	number of females rearing young to weaning	24	28	31	20
F0 offspring (=young F1)	litter size at birth	15.7±2.2 (24)	15.3±2.3 (28)	14.3±2.6* (31)	9.2±4.0*** (20)

Table 4.18 continued overleaf

Table 4.18 continued Summary of reproductive outcome

Generation	Endpoint	control	125 mg/kg/day	300 mg/kg/day	625 mg/kg/day
	group mean birth weights	6.0±0.7	6.0±0.6	6.2±0.6	6.7±0.9**
	live birth index (%)	94	94	96	95
Adult F1	number of animals paired	28	28	28	28
	numbers pregnant	28	27	26	22*
	numbers with live offspring	28	26	25	14
	numbers failing to conceive	0	1	2	6
	number of females dying during lactation/parturition	0	1	1	2
	total litter loss	0	0	0	6 gestation /4 lactation
	number of implantation sites	16.6±2.2	16.1±2.3	13.2±4.3***	4.2±3.1***
	number of females rearing young to weaning	28	26	25	10
F1 offspring (=youngF2)	litter size at birth	15.1±2.4 (28)	14.4±2.4 (27)	12.8±3.3** (25)	4.9±3.0*** (12)
	group mean birth weights	6.2±0.7	6.3±0.7	6.3±0.7	7.2±0.7***
	live birth index (%)	98	92	99	95

n.i. Not investigated,
* p<0.05,
** p<0.01
*** p<0.001, (number of litters in parenthesis)

At 300 mg/kg/day piperazine base, the effects on body weight gain were smaller, although statistically significant in F_0 males (9%), but not in F_0 females. In the F_1 parental generation, bodyweights were significantly reduced in both males and females from week 2, and there was also a slight reduction in food consumption (F_1 females, 9%; F_1 males 9%). However, the food conversion ratios were similar to control values. There was no effect on the number of pregnancies, but a statistically significant reduced litter size at birth was noted in both generations (91% and 85% of control values in F_0-offspring and F_1-offspring, respectively). There was a reduction of implantation sites in F_1 females (Group mean = 13.2 versus. 16.6 in controls). Further, there was a delay in sexual maturation (preputial separation) in F_1 males (not investigated in F_2), but no significant differences in offspring sex ratios. The group mean day of completion of offspring sexual development was also increased in females; although the increase was not statistically significant. It is unclear whether the delayed sexual development could be related to the decreased growth rate (body weight at sexual maturation was decreased by roughly 9%) (**Table 4.19**).

Table 4.19 Group mean day of completion of offspring sexual development, F_1 generation

Dose (mg/kg)	males	females
0	42.3±1.3	42.6±8.6
125	42.1±1.6	44.8±12.1
300	43.5±1.6**	49.5±9.2
625	44.8±1.9***	54.3±11.2***

* p<0.05
** p<0.01
*** p<0.001

At 125 mg/kg/day piperazine base, no effects that could be related to the administration of piperazine were noted. The only clinical signs observed in the study are bright yellow urine in the bedding of all exposed females (all groups), but not in control animals or exposed males.

With respect to effects on reproduction, 5,000 ppm (125 mg/kg/day piperazine base) can be considered as a NOAEL, with 12,000 ppm (300 mg/kg/day) as a LOAEL for this study, with effects mainly on fertility (i.e., reduced pregnancy index and decreased number of implantation sites, although litter losses in F_2 may indicate post implantation losses as well). The lack of effects in the rat developmental toxicity study (Ridgway, 1987b) could be considered to support that effects on fertility are the main effect of piperazine on reproduction in rats. It is possible that the delayed sexual development could be related to the decreased growth (body weights decreased as from week 2 and onwards), as it is therefore not considered of toxicological significance. Relative to the elicitation of toxic effects in the mother animals, there was no reduction of body weight increase in F_0 females given 300 mg/kg/day. For the F_1 females, the body weight gain during gestation was 44%, as compared to 49% for controls. However, their body weights before gestation were 9% lower than the controls. Based on the significantly decreased body weight gain at 300 mg/kg/day in F_0 and F_1 males and in F_1 females, the NOAEL for the adult animals is estimated to be 125 mg/kg/day of piperazine base. Except for the sex organs and the pituitary, histopathological data from other organs are lacking.

4.1.2.9.2 Human reproduction

There is one case report available, describing the birth of a girl with malformed hands and feet as a possible result of piperazine exposure of the mother (Keyer and Brenner, 1988). The mother was treated orally with piperazine adipate (2,100 mg/day or 38 mg/kg/day assuming a body weight of 55 kg) during two 7-days periods, probably encompassing gestation days 41-47 and 55-61. At birth, both hands and one foot displayed malformations. The parents had previously given birth to 2 healthy children (four and seven years before this case). It is difficult to evaluate the possible relationship with the piperazine treatment from this only case.

4.1.2.9.3 Summary of toxicity for reproduction

For reproductive effects, a NOAEL of 125 mg/kg/day and a LOAEL of 300 mg/kg/day piperazine base can be established, with decreased litter size as the main effects. The NOAEL for the adult animals is estimated to be 125 mg/kg/day piperazine base, with body weight

decreases (<10%) at 300 mg/kg/day in the F1-generation and in males of F0. I In the New Zealand rabbit, embryotoxic as well as teratogenic effects were only elicited at doses that also caused overt signs of toxicity in the mother animal (maternal LOAEL 94/ NOAEL 42 mg/kg/day).

Thus, there is a NOAEL/LOAEL of 125/300 mg/kg/day for effects on fertility i.e. reduced pregnancy index, decreased number of implantation sites, and decreased litter size.

Classification Repr. Cat 3; R62-63 is suggested for piperazine.

4.1.3 Risk characterisation

4.1.3.1 General aspects

Piperazine is a solid substance at room temperature and is as a substance as such most often handled as solid flakes or in aqueous solution. The piperazine salts are normally dealt with as particles. The vapour pressure is 39.2 Pa at 22.5°C. The saturated vapour concentration can be calculated to be 1.4 g/m^3 at 22.5°C.

Piperazine is produced at four sites in the EU and is imported from the US. Piperazine is used as an intermediate in the synthesis of a range of chemicals; it is further processed to e.g. human and animal pharmaceuticals, polyurethane catalysts, and bis- and polyamides.

Piperazine is also used in formulations as such or as salts in e.g. pharmaceuticals, gas washer formulations, prepolymers for glues and in other uses.

Two types of NOAEL-values are used in the human health risk characterisation. The NOAEL for reproductive toxicity is obtained from animal studies, whereas the LOAELs for acute toxicity and repeated dose (neuro) toxicity are obtained from human case studies. Since no dose-response relationship can de deduced from such studies the LOAELs may be a ‘low’ rather than ‘lowest’ observed adverse effect level. The latter LOAELs thus already incorporate the concern for interspecies variation, which has been considered in the interpretation of the MOS-values.

4.1.3.1.1 Human exposure

Humans may be exposed to piperazine by inhalation and by dermal exposure in the industry at the manufacture of piperazine and piperazine salts, at the use of piperazine as an intermediate and at the industrial use of formulations containing piperazine.

The occupational exposure scenarios are summarised in **Table 4.20**.

Table 4.20 Occupational exposure to piperazine (reasonable worst case). The scenarios are generic and not related to real industrial sites

	Inhalation exposure		Dermal exposure		Internal exposure (mg/kg/day)			Measured data (mg/m^3)
Scenario	Conc. Vapour (mg/m^3)	Conc dust (mg/m^3)	Derm. exposure ($mg/cm^2/day$)	Exp.Skin area (cm^2)	Inhalation	Dermal	Total	
1A. Production of flakes final handling	3.6	5			1,23		1,23	0.02-1.2
1B. Production of aq. sol final handling	3.6	0			0.51		0.51	0.07-4.4
2A.Production of PZ* salts loading, flakes	3.6	5			1.23		1.23	0.02-1.2
loading, aq.sol.	3.6	0			0.51		0.51	
final handling	0	2.5	0.5	420	0.36	3.00	3.36	0.01-2.4
2B.Synthesis processes with PZ loading, flakes	3.6	5			1.23		1.23	
loading,aq.sol	3.6	0			0.51		0.51	
2C Formulation with PZ salts loading	0	2.5	0.5	420	0.36	3.00	3.36	
3. Use of PZ(flakes) in gas washer loading	3.6	5			1.23		1.23	

*PZ piperazine

For short-term exposure (15 minutes), the concentrations may be twice the above values.

An identified source of consumer exposure to piperazine is via food containing piperazine residues that originates from treatment of animals with pharmaceuticals containing piperazine. 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). The MRLs established for piperazine result in a maximum daily intake of 0.05 mg/kg bw/day. Therefore this use is not further addressed here.

Contribution to consumer exposure from other sources is considered negligible.

Human exposure via the environment, i.e., food, water and air, has been estimated by the EUSES model for the release of piperazine from industrial processes and from manure. The predicted total daily intake via the environment (mg/kg/day) are summarised in **Table 4.21**.

Table 4.21 Predicted total daily intake via the environment (mg/kg/day) (EUSES).

Site	Life cycle stage / use pattern	Total local daily intake (mg/kg/day)	Comment
A	Production	$3.5 \cdot 10^{-5}$	Site specific
C	Production	0.002	Site specific
E	Processing	0	Site specific
F	Processing/formulation	0	Site specific
G	Processing/formulation	$3.5 \cdot 10^{-5}$	Generic local formulation
H	Formulation	0.008	Site specific
Gas washer	6 processing	0.189	Generic local EUSES
Pharmaceuticals	7 private use	$7.97 \cdot 10^{-7}$	Generic local EUSES
Groundwater- Manure from piperazine treated animals	8	$2.94 \cdot 10^{-8}$	

The regional total daily intake in humans is calculated by EUSES to $2.4 \cdot 10^{-5}$ mg/kg /day.

The predominant sources of human exposure to piperazine via the environment (as estimated by EUSES) are via drinking water (the major part), with minor contributions from fish and root crops, in most industrial scenarios. For Scenario 8; "Manure from piperazine treated animals", there is a different route of emission. For this latter scenario, root crops and water are the predominant sources.

4.1.3.1.2 Toxicokinetics

In the pig, 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. However, no data on dermal uptake have been located. The principal route of excretion of piperazine and its metabolites is via urine, with a minor fraction recovered from faeces (16%). However, about one forth of a single administered oral dose is retained in the tissues after 7 days, some of which seems to consist of unidentified conversion products.

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 also here remain unknown. Based on the data above, an oral absorption of 100% is used, whereas default absorption values of 100% are assumed for dermal and respiratory exposure.

In the presence of nitrite, the *in vivo* formation of small amounts of nitrosated products from piperazine has been demonstrated to occur in the gastrointestinal tract of experimental animals as well as in humans.

4.1.3.1.3 Acute toxicity

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 located. Although the lethal dose in humans has not been established, clinical experience indicates the same to be true for humans. However, there are findings of EEG

changes in 37% of 89 children administered 90-130 mg/kg piperazine base (two doses during one day), corroborated by the proposed GABA receptor agonism exerted by piperazine. Since more severe neurotoxicity symptoms can appear after exposure to higher doses (divided under several days), a LOAEL of 110 mg/kg for neurotoxicity in humans after acute exposure is proposed.

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.

Exposure to piperazine and its 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.

4.1.3.1.4 Repeated exposure

A NOAEL of 25 mg/kg/day of piperazine base for liver toxicity in the Beagle dog can be established.

However, adequate chronic bioassays are not available, and the fact that none of the systematic experimental studies reported neurotoxic effects is a cause for serious concern. Such effects, that occasionally are serious, have been well documented in human clinical practice, and have also been described by veterinarians in rabbits, dogs, cats, tigers, horses, the puma, and sea lions. For previously healthy humans, a LOAEL of about 30 mg piperazine base/kg/day can be established for a limited 3-7 day's treatment period. Based on existing data, a NOAEL cannot be established for neurotoxicity induced by piperazine, neither in a sensitive animal species nor in humans upon long-term exposure.

The human neurotoxicity data has been given preference over the dog-based NOAEL cited above. The reasons are the higher relevance of studies in humans (e.g., as regards human sensitivity to the toxic effect) as compared to studies in animals, and the lower need for assessment factors when basing the risk characterisation on studies in humans as compared to studies in animals. As such, neurotoxicity could also be considered of higher concern than mild hepatic effects. Therefore, the LOAEL for neurotoxic effects obtained from the human case studies will be used in the risk characterisation, and the evaluation of the MOS has to consider that a human LOAEL is used. Also, the effects of lower doses than 30 mg/kg/day have not been studied, so this dose may not be the lowest LOAEL, which should be kept in mind when interpreting the MOS.

4.1.3.1.5 Genotoxic potential

Studies conducted *in vitro,* as well as *in vivo* indicate that piperazine does not induce point mutations or chromosome aberrations. Due to the likelihood of exposure to other clastogenic chemicals, the significance of the modest increase in micronuclei seen in exposed workers cannot be ascertained. However, nitroso-piperazines that can be formed by nitrosation of piperazine *in vivo* demonstrate clear genotoxic properties.

4.1.3.1.6 Carcinogenicity

There is no clear indication that piperazine is carcinogenic based on animal studies, investigations in humans, or from supporting data. In view of lack of genotoxic action, it appears unlikely that piperazine as such poses a carcinogenic risk.

The two nitrosated derivatives of piperazine, N-mononitrosopiperazine (NPZ) as well as N,N'-dinitrosopiperazine (DNPZ) have been found to be carcinogenic in rodents.

In the study conducted by Love and Lijinski (1977), where MRC-rats were administered NPZ at a daily average dose of 27 and 54 mg/kg, a dose response relationship was found with respect to the induction of tumours in the nasal cavity. Linear extrapolation based on the incidence of tumours in the nasal cavities in MRC rats upon oral administration (Love and Lijinski, 1977), gives a carcinogenic potency (slope factor) for lifetime cancer risk of approximately 0.01 $(mg/kg/day)^{-1}$ for this species.

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. It is concluded 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. This endpoint will only be commented on in the risk characterisation for workers.

4.1.3.1.7 Toxicity for reproduction

For reproductive effects of piperazine base, 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.

A summary of end-points brought forward to the risk characterisation for qualitative evaluation is presented in **Table 4.22** below. In addition, the worker risk characterisation contains the end-points acute toxicity and carcinogenicity.

Table 4.22 Summary of effects brought forward to the risk characterisation.

End-point	NOAEL/LOAEL	Comments
Acute toxicity	LOAEL 110 mg/kg	based on human case studies
Irritation	not applicable	
Dermal sensitisation	not applicable	
Respiratory sensitisation	not applicable	
Repeated dose neurotoxicity	LOAEL 30 mg/kg/day	based on human case studies
Reproductive toxicity	NOAEL 125 mg/kg/day	based on a rat study

4.1.3.2 Workers

Assuming that oral exposure is prevented by good hygiene practice the risk characterisation for workers is limited to the dermal and inhalation routes of exposure.

For the highly irritating piperazine base (anhydrate and hexahydrate), it is assumed that PPE is used and prevents all dermal exposure. Thus, only inhalation exposure is considered for

piperazine base. For the piperazine salts, which are not irritating, the calculations are based on the assumption that no PPE is used, thus allowing both inhalation and dermal exposure.

4.1.3.2.1 Acute toxicity

Although the LD_{50} –levels indicate a relatively low level of oral acute toxicity (LD_{50} 1-5 g/kg bw) (acute respiratory studies are not available, but further testing is not recommended because of the irritant/corrosive nature of piperazine), the neurotoxicity normally observed after several days of exposure also may appear after shorter exposure periods. EEG-changes were observed in 37% of children exposed during one day to two doses of totally 110 mg/kg piperazine base, thus giving a LOAEL of 110 mg/kg.

In setting a minMOS, there is no need for assessment factors for inter- or intraspecies variation, or for duration. Considering that only EEG-changes were observed, but no visible signs, no factor is suggested for severity. However, as the effect level is a LOAEL, and there is a lack of a proper dose-response curve, an assessment factor of 5 is proposed to cover for this fact. The total minMOS for acute toxicity is, thus, 5.

Based on exposure levels of up to 3.4 mg/kg/day, and a LOAEL of 110 mg/kg, all MOS-values are greater than 32, which compared with a minMOS of 5 gives no concern for acute toxicity.

Hence **conclusion (ii)** is recommended.

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

4.1.3.2.2 Skin and eye irritation, and corrosion

No NOAEL can be estimated for skin and eye irritation, and 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)** is warranted.

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

4.1.3.2.3 Skin sensitisation

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)** is warranted.

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

4.1.3.2.4 Occupational Asthma

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)** is warranted. It is unclear to what extent normal PPE can protect against sensitisation.

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

4.1.3.2.5 Repeated Dose Toxicity

The internal worker exposure during normal work has been estimated to be between 0.5 and 3.4 mg /kg/day for an 8-hour day. The bioavailability, in all scenarios, is assumed to be 100%, both for exposure via inhalation and for dermal exposure.

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, with severe signs of neurotoxicity, although the effects are reversible. Based on the severity of the effect (warranting an assessment factor of 2) as well as the lack of a proper dose-response curve (warranting an assessment factor of 5), a general minMOS of 10 is proposed for neurotoxicity in workers.

In addition, a NOAEL of 25 mg/kg/day of piperazine base for liver toxicity in the Beagle dog can be established, although risk characterisation is only performed for neurotoxicity.

Table 4.23 MOS for Repeated Dose Toxicity (neurotoxicity) for each worker exposure scenario. I=Inhalation, D=Dermal

Scenario	Internal exposure (mg/kg/day) I + D**	LOAEL* (mg/kg/day)	MOS	Concl.
1A.Production ofPZ flakes final handling	1.2	30	25	(ii)
1B.Production ofPZ aq. sol final handling	0.5	30	60	(ii)
2A.Production of PZ salts loading, flakes	1.2	30	25	(ii)
loading, aq.sol.	0.5	30	60	(ii)
final handling	0.4+3=3.4	30	8.8	(iii)
2B.Synthesis processes with PZ loading, flakes	1.2	30	25	(ii)
loading,aq.sol	0.5	30	60	(ii)

Table 4.23 continued overleaf

Table 4.23 continued MOS for Repeated Dose Toxicity (neurotoxicity) for each worker exposure scenario. I=Inhalation, D=Dermal

Scenario	Internal exposure (mg/kg/day) I + D**	LOAEL* (mg/kg/day)	MOS	Concl.
2C Formulation with PZ salts loading	0.4+3=3.4	30	8.8	(iii)
3. Use of PZ(flakes) in gas washer loading	1.2	30	25	(ii)

* LOAEL derived from human case studies.
** A dermal absorption of 100 % is assumed.

Based on the above derived MOSs **conclusion (iii)** is recommended for production of piperazine salts (final handling) and formulation with piperazine salts (loading).

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

Some current (typical) exposure levels are generally in the same order as the RWC-levels, whereas when also considering actual time of exposure, the above internal exposure values are probably 2-4 times higher than typical values. Thus, under typical exposure conditions or when appropriate PPE is being used, there would be no concern for this endpoint.

4.1.3.2.6 Carcinogenicity

There is no clear indication that piperazine is carcinogenic based on animal studies, investigations in humans, or from supporting data. In view of lack of genotoxic action, it appears unlikely that piperazine as such poses a carcinogenic risk.

There seems to be an additional cancer risk due to the formation of 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. It is concluded 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 (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

4.1.3.2.7 Reproductive toxicity

The internal worker exposure during normal work has been estimated to be between 0.5 and 3.4 mg/kg/day for an 8-hour day. The bioavailability, in all scenarios, is assumed to be 100%, both for exposure via inhalation and dermal exposure.

In **Table 4.24**, the MOS is calculated for a NOAEL of 125 mg/kg/day for effects on fertility (i.e., reduced pregnancy index, decreased number of implantation sites, and a decreased litter size in rats). In setting the minMOS, the interspecies variation (animal to human; 10), the intraspecies variation (in the human population; 3), and the severity of the effect (reduced fertility at a dose twice the NOAEL; 2) need to be considered. A general minMOS of 60 is proposed, with some flexibility with borderline cases because of the likely overestimated dermal absorption (default 100%).

Table 4.24 MOSs for reproductive toxicity for each worker exposure scenario

Scenario	Total internal exposure (mg/kg/day) I + D**	NOAEL* (mg/kg/day)	MOS	Concl.
8-hour exposure				
1A. Production of flakes final handling	1.2	125	104	(ii)
1B.Production of aq.sol final handling	0.5	125	250	(ii)
2A Production of PZ salts loading, flakes	1.2	125	104	(ii)
loading, aq.sol.	0.5	125	250	(ii)
final handling	0.4 + 3.0 = 3.4	125	37	(iii)
2B Synthesis processes with PZ loading, flakes	1.2	125	104	(ii)
loading, aq.sol	0.5	125	250	(ii)
2C Formulation with PZ salts Loading	0.4 + 3 = 3.4	125	37	(iii)
3 Use of PZ(flakes) in gas washer Loading	1.2	125	104	(ii)

* NOAEL derived from a two-generation rat study.
** A dermal absorption of 100% is assumed.

Based on the above derived MOSs **conclusion (iii)** is recommended production of piperazine salts (final handling) and formulation with piperazine salts (loading).

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

Some current (typical) exposure levels are generally in the same order as the RWC-levels, whereas when also considering actual time of exposure, the above internal exposure values are probably 2-4 times higher than typical values. Thus, already at typical exposure conditions, or if using appropriate PPE, there would be no concern for this end-point.

4.1.3.3 Consumers

The use of piperazine in veterinary medicine as an anthelmintic in pigs and poultry (including laying hens) is already covered by 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. Therefore this use is not further addressed here.

4.1.3.4 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.

4.1.3.4.1 Acute toxicity

When calculating MOS for a LOAEL of 110 mg/kg for acute neurotoxicity signs, the lowest MOS is about 4,800, leading to no concern for this endpoint.

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

4.1.3.4.2 Repeated Dose Toxicity

A LOAEL for neurotoxicity in adults and children of 30 mg/kg/day of piperazine base has been obtained from 3-7 days medical treatments of humans. However, since lower doses have not been studied, this may not be the lowest possible LOAEL. In addition, a NOAEL of 25 mg/kg/day of piperazine base for liver toxicity in the Beagle dog can be established, although risk characterisation is only performed for neurotoxicity.

Table 4.25 MOSs for Repeated Dose Toxicity for humans exposed via the environment

Local Scenario		Total local daily intake (mg/kg/day)	LOAEL* (mg/kg/day)	MOS	Concl.
A	Production	$9.1 \cdot 10^{-5}$	30	$3.3 \cdot 10^{5}$	(ii)
(B)**	Production	not applicable	30		
C	Production	0.002	30	15,000	(ii)
(D)**	Production, processing and formulation	not applicable	30		
E	Processing	$5.6 \cdot 10^{-5}$	30	$5.4 \cdot 10^{5}$	(ii)
F	Processing and formulation	$5.6 \cdot 10^{-5}$	30	$5.4 \cdot 10^{5}$	(ii)
G	Processing and formulation	$9.1 \cdot 10^{-5}$	30	$3.3 \cdot 10^{5}$	(ii)
H	Formulation	0.009	30	3,333	(ii)
EUSES Scenario 6.	Gas washer	0.0231	30	1,304	(ii)
EUSES Scenario 7	Private use pharmaceuticals	$4.79 \cdot 10^{-5}$	30	6,680	(ii)
EUSES Scenario 8	Groundwater-Manure from piperazine treated animals	$5.52 \cdot 10^{-3}$	30	5,430	(ii)
Regional (EUSES)		$2.4 \cdot 10^{-5}$	30	$1.25 \cdot 10^{6}$	(ii)

* LOAEL derived from human case studies

** Site B and site D are located at the sea and at an estuary, and are therefore not relevant for assessment of human exposure via the environment.

In the present assessment, intake via drinking water and fish are the major exposure routes. Based on the above MOS, there is no concern for this end-point.

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

4.1.3.4.3 Reproductive toxicity

When the MOS is calculated for a NOAEL of 125 mg piperazine base/kg/day for effects on fertility in rats (i.e., reduced pregnancy index, decreased number of implantation sites, and a decreased litter size), all MOSs are higher than 5,400, which is the value for the gas washer scenario.

Based on the above MOS there is no concern for this end-point.

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

4.1.3.5 Combined exposure

Combined occupational exposure, consumers' exposure and environmental exposure will not influence the characterisation of the risks, which are outlined in 4.1.3.2, 4.1.3.3 and 4.1.3.4.

4.2 HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES)

No concern is recognised for explosivity, flammability and oxidising potential for occupational, consumer and humans exposed via the environment populations. Hence, **conclusion (ii)** is recommended.

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

5 RESULTS

5.1 GENERAL

Piperazine is used as intermediate in the synthesis of a range of chemicals, further processed to human and animal drugs, polyurethane catalysts, bis- and polyamides and other uses. Piperazine is also used as such or as salts in pharmaceuticals, gas washer liquid formulations, prepolymer for glues and other industrial and non-industrial uses. Piperazine is produced at four sites in the EU and imported from the US. The tonnage of piperazine has been estimated by using the figures for production, import, and export reported for 1997.

Piperazine has very high water solubility, 150 g/l, and an octanol/water-partition coefficient of -1.24. The substance is slowly degraded in water and soil, but rapidly photolysed in the atmosphere. The potential for bioaccumulation is considered to be low. Piperazine will almost totally be distributed to the aquatic phase in the STP. Adsorption studies in soil indicate that sorption in this compartment is higher than in the STP, probably due to the presence of negatively charged clay mineral particles that attract piperazine that is positively charged at neutral pH. K_d was determined to be 7.9-20 in three different soils.

The substance flow of piperazine has been described for nine point sources and two scenarios with more diffuse emissions; end product use of pharmaceuticals and gas washer formulations. One local scenario for agricultural soil has been constructed for the use of piperazine as anthelmintic in domestic animals.

Of the total tonnage for 1997, approximately 75% was specified with regard to use pattern. According to recently submitted figures for 2002, the total production in the EU has increased, but since a larger portion of the production volumes is exported outside the EU, the total tonnage has decreased compared to 1997. For 2002 a larger portion (97%) of the tonnage was specified, but the proportional distribution between different use patterns had not significantly changed. Therefore, the scenarios based on the 1997 figures are still considered to be reasonable.

5.2 ENVIRONMENT

5.2.1 Aquatic compartment

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, the local formulation site H, and for 21 out of 33 local scenarios for down-stream users of gas washer formulations the PEC/PNEC ratios are >1. 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.

5.2.2 Terrestrial compartment

Conclusion (ii) There is at present no need for further information and/or testing and 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.

5.2.3 Atmosphere

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

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

5.2.4 Secondary poisoning

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

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

5.3 HUMAN HEALTH

The results summarised here are presented in detail in Section 4.

The ratio between NOAELs or LOAELs and exposure levels for different human populations and scenarios has been used to derive the MOS. The lowest and most reliable NOAELs or LOAELs established have been used. The LOAELs for acute toxicity and repeated dose (neuro) toxicity are calculated based on studies in humans, whereas the NOAEL for reproductive toxicity is based on studies in animals.

Human populations exposed to piperazine are: workers, consumers exposed via residues in pork meat and chicken's eggs, and indirect exposure of humans via the environment.

5.3.1 Workers

Six occupational exposure scenarios have been considered, concerning exposure during production of piperazine flakes, production of piperazine salts and industrial use of piperazine in syntheses.

Worst-case exposure is assumed for the scenarios on production and industrial use, by using monitored data when available, and otherwise modelled values for inhalation exposure and dermal exposure.

There are little quantitative and qualitative information available on technical control measures and on the use of personal protective equipment during production and processing to establish their efficiency. However, because of the irritant properties of piperazine base (anhydrate and hexahydrate) (classified with R34) it is assumed that PPE is used when these substances are handled, thus excluding potential for dermal exposure.

5.3.1.1 Acute toxicity

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

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 a total dose of 110 mg/kg piperazine base. Based on exposure levels of up to 3.4 mg/kg/day, and a LOAEL of 110 mg/kg, there is no concern for acute toxicity.

5.3.1.2 Skin and eye irritation, and corrosion

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

No NOAEL can be estimated for skin and eye irritation, and 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)** is warranted.

5.3.1.3 Skin sensitisation

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

Worker exposure to piperazine salts by the dermal route has been estimated to be up to 0.5 mg/cm^2/day. It is, therefore, due to the sensitising nature of piperazine concluded that piperazine represents a risk for workers concerning skin sensitisation.

5.3.1.4 Occupational Asthma

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

The external worker exposure has been estimated to be up to 8.6 mg/m^3 (vapour and dust) for an 8-hour day and even higher during peak exposure. Based on the clearly sensitising potential it is concluded that piperazine represents a risk for workers concerning occupational asthma for an 8-hour exposure.

5.3.1.5 Repeated Dose toxicity

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

The internal worker exposure has been estimated to be 0.4-3.4 mg/kg /day for an 8-hour day exposure. Based on the LOAEL for neurotoxicity in adults of 30 mg/kg/day of piperazine base in medical treatments of humans, it is conducted that piperazine represents a risk for workers (production of piperazine salts - final handling, and formulation with piperazine salts-loading) concerning repeated dose toxicity.

5.3.1.6 Carcinogenicity

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

There seems to be an additional cancer risk due to the formation of 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. It is concluded 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.

5.3.1.7 Reproductive toxicity

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

The internal worker exposure has been estimated to be between 0.4-3.4 mg/kg/day for an 8-hour day. Based on the derived MOSs it is concluded that piperazine represents a risk for workers (production of piperazine salts - final handling, and formulation with piperazine salts-loading) concerning reproductive toxicity.

5.3.2 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.

5.3.3 Humans exposed via the environment

5.3.3.1 Repeated dose toxicity and reproductive toxicity

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

The MOSs indicate that there are no concerns for humans exposed via the environment.

5.3.4 Combined exposure

Combined environmental exposure, consumers' exposure and occupational exposure will not influence the characterisation of the risks, which are outlined above.

5.4 HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES)

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

No concern is recognised for explosivity, flammability and oxidising potential for occupational, consumer and humans exposed via the environment populations.

5.5 DATA GAPS IN RELATION TO "BASE SET"

The following information related to Article 9:2, Council Regulation 793/93/EEC is lacking:

- Flammability

- Acute toxicity: administered by inhalation with determination of concentration

5.5.1 Rapporteurs comments to data gaps

Although adequate acute respiratory studies are not available, further testing is not recommended because of the irritant/corrosive nature of piperazine.

Although a regular auto-flammability test is not available, further testing is not required since sufficient information is available to conclude that auto-flammability is not a concern, and IND has been granted derogation according to Article 9:3 (Council Regulation 793/93/EEC).

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ABBREVIATIONS

ADI	Acceptable Daily Intake
AF	Assessment Factor
ASTM	American Society for Testing and Materials
ATP	Adaptation to Technical Progress
AUC	Area Under The Curve
B	Bioaccumulation
BBA	Biologische Bundesanstalt für Land- und Forstwirtschaft
BCF	Bioconcentration Factor
BMC	Benchmark Concentration
BMD	Benchmark Dose
BMF	Biomagnification Factor
BOD	Biochemical Oxygen Demand
bw	body weight / *Bw*, *bw*
C	Corrosive (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)
CA	Chromosome Aberration
CA	Competent Authority
CAS	Chemical Abstract Services
CEC	Commission of the European Communities
CEN	European Standards Organisation / European Committee for Normalisation
CEPE	European Committee for Paints and Inks
CMR	Carcinogenic, Mutagenic and toxic to Reproduction
CNS	Central Nervous System
COD	Chemical Oxygen Demand
CSTEE	Scientific Committee for Toxicity, Ecotoxicity and the Environment (DG SANCO)
CT_{50}	Clearance Time, elimination or depuration expressed as half-life
d.wt	dry weight / dw
dfi	daily food intake
DG	Directorate General
DIN	Deutsche Industrie Norm (German norm)
DNA	DeoxyriboNucleic Acid
DOC	Dissolved Organic Carbon
DT50	Degradation half-life or period required for 50 percent dissipation / degradation
DT90	Period required for 90 percent dissipation / degradation
E	Explosive (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)
EASE	Estimation and Assessment of Substance Exposure Physico-chemical properties [Model]

EbC50	Effect Concentration measured as 50% reduction in biomass growth in algae tests
EC	European Communities
EC10	Effect Concentration measured as 10% effect
EC50	median Effect Concentration
ECB	European Chemicals Bureau
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
ECVAM	European Centre for the Validation of Alternative Methods
EDC	Endocrine Disrupting Chemical
EEC	European Economic Communities
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINCS	European List of New Chemical Substances
EN	European Norm
EPA	Environmental Protection Agency (USA)
ErC50	Effect Concentration measured as 50% reduction in growth rate in algae tests
ESD	Emission Scenario Document
EU	European Union
EUSES	European Union System for the Evaluation of Substances [software tool in support of the Technical Guidance Document on risk assessment]
F(+)	(Highly) flammable (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)
FAO	Food and Agriculture Organisation of the United Nations
FOCUS	Forum for the Co-ordination of pesticide fate models and their use.
FELS	Fish Early Life Stage
foc	Organic carbon factor (compartment depending)
GLP	Good Laboratory Practice
HEDSET	EC/OECD Harmonised Electronic Data Set (for data collection of existing substances)
HELCOM	Helsinki Commission -Baltic Marine Environment Protection Commission
HPLC	High Pressure Liquid Chromatography
HPVC	High Production Volume Chemical (> 1000 tonnes/annum)
IARC	International Agency for Research on Cancer
IC	Industrial Category
IC50	median Immobilisation Concentration or median Inhibitory Concentration
ILO	International Labour Organisation
IPCS	International Programme on Chemical Safety
ISO	International Organisation for Standardisation
IUCLID	International Uniform Chemical Information Database (existing substances)
IUPAC	International Union for Pure and Applied Chemistry
JEFCA	Joint FAO/WHO Expert Committee on Food Additives

JMPR	Joint FAO/WHO Meeting on Pesticide Residues
Koc	organic carbon normalised distribution coefficient
Kow	octanol/water partition coefficient
Kp	solids-water partition coefficient
L(E)C50	median Lethal (Effect) Concentration
LAEL	Lowest Adverse Effect Level
LC50	median Lethal Concentration
LD50	median Lethal Dose
LEV	Local Exhaust Ventilation
LLNA	Local Lymph Node Assay
LOAEL	Lowest Observed Adverse Effect Level
LOEC	Lowest Observed Effect Concentration
LOED	Lowest Observed Effect Dose
LOEL	Lowest Observed Effect Level
MAC	Maximum Allowable Concentration
MATC	Maximum Acceptable Toxic Concentration
MC	Main Category
MITI	Ministry of International Trade and Industry, Japan
MOE	Margin of Exposure
MOS	Margin of Safety
MW	Molecular Weight
N	Dangerous for the environment (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC
NAEL	No Adverse Effect Level
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
NOEC	No Observed Effect Concentration
NTP	National Toxicology Program (USA)
O	Oxidising (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)
OC	Organic Carbon content
OECD	Organisation for Economic Cooperation and Development
OEL	Occupational Exposure Limit
OJ	Official Journal
OSPAR	Oslo and Paris Convention for the protection of the marine environment of the Northeast Atlantic
P	Persistent
PBT	Persistent, Bioaccumulative and Toxic

PBPK	Physiologically Based PharmacoKinetic modelling
PBTK	Physiologically Based ToxicoKinetic modelling
PEC	Predicted Environmental Concentration
pH	logarithm (to the base 10) of the hydrogen ion concentration $\{H^+\}$
pKa	logarithm (to the base 10) of the acid dissociation constant
pKb	logarithm (to the base 10) of the base dissociation constant
PNEC	Predicted No Effect Concentration
POP	Persistent Organic Pollutant
PPE	Personal Protective Equipment
QSAR	(Quantitative) Structure-Activity Relationship
R phrases	Risk phrases according to Annex III of Directive 67/548/EEC
RAR	Risk Assessment Report
RC	Risk Characterisation
RfC	Reference Concentration
RfD	Reference Dose
RHO	Bulk density of the solid phase (soil, sediment, susp. matter)
RNA	RiboNucleic Acid
RPE	Respiratory Protective Equipment
RWC	Reasonable Worst-Case
S phrases	Safety phrases according to Annex IV of Directive 67/548/EEC
SAR	Structure-Activity Relationships
SBR	Standardised birth ratio
SCE	Sister Chromatic Exchange
SCHER	Scientific Committee on Health and Environmental Risks
SDS	Safety Data Sheet
SETAC	Society of Environmental Toxicology And Chemistry
SIMPLETREAT	Fugacity model for simulation of the fate of chemicals in waste water treatment plants. Based on partition coefficient octanol-water, vapour pressure and biodegradability
SNIF	Summary Notification Interchange Format (new substances)
SSD	Species Sensitivity Distribution
STP	Sewage Treatment Plant
T(+)	(Very) Toxic (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)
TDI	Tolerable Daily Intake
TG	Test Guideline
TGD	Technical Guidance Document
TNsG	Technical Notes for Guidance (for Biocides)

TNO	The Netherlands Organisation for Applied Scientific Research
ThOD	Theoritical Oxygen Demand
TWA	Time Weighted Average
UC	Use Category
UDS	Unscheduled DNA Synthesis
UN	United Nations
UNEP	United Nations Environment Programme
US EPA	Environmental Protection Agency, USA
UV	Ultraviolet Region of Spectrum
UVCB	Unknown or Variable composition, Complex reaction products of Biological material
vB	very Bioaccumulative
VOC	Volatile Organic Compound
vP	very Persistent
vPvB	very Persistent and very Bioaccumulative
v/v	volume per volume ratio
w/w	weight per weight ratio
WHO	World Health Organisation
WWTP	Waste Water Treatment Plant
Xn	Harmful (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)
Xi	Irritant (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)

Appendix 1 EASE

EASE 1

Tue Oct 15 15:54:24 2002

The user name is Leif B

The name of the substance is PZ

The temperature of the process is 20

The physical-state is solid

Dust-inhalation is false

Mobile-solid is true

Solid-vp is true

The exposure-type is gas/vapour/liquid aerosol

The use-pattern is Non-dispersive use

The pattern-of-control is LEV

The status-vp-value is Measured at a different temp.

The vp-value of the substance is 0.0392

The vapour pressure value at the measurement temperature is 0.0392

The calculated vapour pressure value is 0.0335

The vp-value of the substance is 0.0335

The measurement-temperature is 22.5

The volatility of the substance is low

The ability-airborne-vapour of the substance is low

CONCLUSION: The predicted gas/vapour/liquid aerosol exposure to PZ is 0.5-1.0 ppm

Inhalation exposure to the gas, vapour or liquid aerosol of PZ at a process temperature of 20 is determined by :

- the pattern of use (Non-dispersive use),
- the pattern of control (LEV)
- and the ability of the substance to become airborne (low)
- resulting in an exposure range of 0.5-1.0 ppm

EASE 2

Tue Oct 15 16:02:04 2002

The user name is Leif B

The name of the substance is PZ

The temperature of the process is 20

The physical-state is solid

Dust-inhalation is true

Mobile-solid is true

Solid-vp is true

The exposure-type is dust

The particle-size is Respirable

The operations is Dry manipulation

The dust-type is Non-fibrous

Aggregates is false

The pattern-of-control is LEV present

CONCLUSION: The predicted dust exposure to PZ is 2-5 mg/cubic metre

Dust exposure to a non-fibrous solid is determined by:

- the process operations (Dry manipulation),
- whether the solid aggregates readily (No)
- and the pattern of control (LEV present),
- resulting in an exposure range of 2-5 mg/cubic metre

EASE 3

Tue Oct 15 16:03:09 2002

The user name is Leif B

The name of the substance is PZ

The temperature of the process is 20

The physical-state is solid

Ddust-inhalation is false

Mobile-solid is true

Solid-vp is true

The exposure-type is dermal

The use-pattern is Non-dispersive use

The pattern-of-control is Direct handling

The contact-level is Intermittent

CONCLUSION: The predicted dermal exposure to PZ is 0.1-1 mg/square cm/day

Dermal exposure to a substance which is directly handled is determined by the

- use pattern (Non-dispersive use) and the contact level (Intermittent), resulting in an exposure range of 0.1-1 mg/square cm/day

EASE 4

Tue Oct 15 16:07:29 2002

The user name is Leif B

The name of the substance is PZ

The temperature of the process is 20

The physical-state is solid

Ddust-inhalation is true

Mobile-solid is true

Solid-vp is true

The exposure-type is dust

The particle-size is Respirable

The operations is Dry manipulation

The dust-type is Non-fibrous

Aggregates is false

The pattern-of-control is LEV absent

CONCLUSION: The predicted dust exposure to PZ is 5-50 mg/cubic metre

Dust exposure to a non-fibrous solid is determined by:

- the process operations (Dry manipulation),
- whether the solid aggregates readily (No)
- and the pattern of control (LEV absent),
- resulting in an exposure range of 5-50 mg/cubic metre

EASE 5

Tue Oct 15 16:12:04 2002

The user name is Leif B

The name of the substance is PZ

The temperature of the process is 20

The physical-state is solid

Dust-inhalation is false

Mobile-solid is true

Solid-vp is true

The exposure-type is dermal

The use-pattern is Wide dispersive use

The pattern-of-control is Direct handling

The contact-level is Intermittent

CONCLUSION: The predicted dermal exposure to PZ is 1-5 mg/square cm/day

Dermal exposure to a substance which is directly handled is determined by the

- use pattern (Wide dispersive use) and the contact level (Intermittent), resulting in an exposure range of 1-5 mg/square cm/day

EASE 6

Wed Jan 22 11:57:18 2003

The user name is Leif Bengtsson

The name of the substance is PZ

The temperature of the process is 20

The physical-state is liquid

The exposure-type is gas/vapour/liquid aerosol

Aerosol-formed is false

The use-pattern is Non-dispersive use

The pattern-of-control is Direct handling

The direct-handling is Direct handling with dilution ventilation

The status-vp-value is Measured at a different temp.

The vp-value of the substance is 0.0392

The vapour pressure value at the measurement temperature is 0.0392

The calculated vapour pressure value is 0.0335

The vp-value of the substance is 0.0335

The measurement-temperature is 22.5

The volatility of the substance is low

The ability-airborne-vapour of the substance is low

CONCLUSION: The predicted gas/vapour/liquid aerosol exposure to PZ is 10-20 ppm

Inhalation exposure to the gas, vapour or liquid aerosol of PZ at a process temperature of 20 is directly handled is determined by :

- the pattern of use (Non-dispersive use),
- the ability of the substance to become airborne (low)
- and the level of control applied to the handling (Direct handling with dilution ventilation)

resulting in an exposure range 10-20 ppm

EASE 7

Wed Jan 22 12:02:27 2003

The user name is Leif Bengtsson

The name of the substance is PZ

The temperature of the process is 20

The physical-state is liquid

The exposure-type is dermal

The use-pattern is Wide dispersive use

The pattern-of-control is Direct handling

The contact-level is Intermittent

CONCLUSION: The predicted dermal exposure to PZ is 1-5 mg/square cm/day

Dermal exposure to a substance which is directly handled is determined by the use pattern (Wide dispersive use) and the contact level (Intermittent), resulting in an exposure range of 1-5 mg/square cm/day

EASE 8

Wed Oct 16 14:32:23 2002

The user name is Leif B

The name of the substance is PZ

The temperature of the process is 20

The physical-state is liquid

The exposure-type is dermal

The use-pattern is Non-dispersive use

The pattern-of-control is Direct handling

The contact-level is Incidental

CONCLUSION: The predicted dermal exposure to PZ is 0-0.1 mg/square cm/day

Dermal exposure to a substance which is directly handled is determined by the use pattern (Non-dispersive use) and the contact level (Incidental), resulting in an exposure range of 0-0.1 mg/square cm/day

European Commission

EUR 21642 EN European Union Risk Assessment Report
Piperazine, Volume 56

Editors: S.J. Munn, R. Allanou, K. Aschberger, O. Cosgrove, S. Pakalin, A. Paya-Perez, G. Pellegrini, B. Schwarz-Schulz, S. Vegro.

Luxembourg: Office for Official Publications of the European Communities

2005 – IX pp., 159 pp. – 17.0 x 24.0 cm

Environment and quality of life series

The report provides the comprehensive risk assessment of the substance piperazine. It has been prepared by Sweden in the frame of Council Regulation (EEC) No. 793/93 on the evaluation and control of the risks of existing substances, following the principles for assessment of the risks to humans and the environment, laid down in Commission Regulation (EC) No. 1488/94.

The evaluation considers the emissions and the resulting exposure to the environment and the human populations in all life cycle steps. Following the exposure assessment, the environmental risk characterisation for each protection goal in the aquatic, terrestrial and atmospheric compartment has been determined. For human health the scenarios for occupational exposure, consumer exposure and humans exposed via the environment have been examined and the possible risks have been identified.

The environmental risk assessment for Piperazine concludes that there is at present concern for the aquatic ecosystem, while no concerns were identified for the atmosphere, terrestrial ecosystem or for microorganisms in the sewage treatment plant from sources of piperazine covered by Regulation 793/93.

The human health risk assessment for piperazine concludes that there is at present concern for workers. For consumers and humans exposed via the environment the risk assessment concludes that there is no risk.
The exposure of consumers due to use of piperazine in veterinary medicine as an anthelmintic in pigs and poultry is regulated by Council Regulation (EEC) No. 2377/90 with the establishment of Maximum Residue Limits.

The conclusions of this report will lead to risk reduction measures to be proposed by the Commission's Committee on risk reduction strategies set up in support of Council Regulation (EEC) 793/93.

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European Commission – Joint Research Centre
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European Union Risk Assessment Report

piperazine

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