RISK ASSESSMENT

Methenamine

CAS-No.: 100-97-0

EINECS-No.: 202-905-8

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FINAL APPROVED VERSION

Information on the rapporteur

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The first draft of the Human Health Section of the Comprehensive Risk Assessment Report **Methenamine**, a substance chosen from the EU 2nd Priority List in 1995 was distributed for preliminary written procedure in September 2004, for the in-depth discussion at the TC NES I´05 (March 2005) and for a last-visit discussion at TC NES III´05 (September 2005).

The first draft of the Environment Section of the Comprehensive Risk Assessment Report was distributed for preliminary written procedure in February 2005 (TC NES I´05), for in-depth at TCNES II'05 in June 2005 and for a last-visit discussion at TC NES IV`05 (November 2005).

This document is the revised Human Health Section and revised Environment Section of the Comprehensive Risk Assessment Report.

The Human Health Section was distributed for the final written approval (December 2005), updated based on additional written comments received till February 2006 and the Environment Section which was distributed for the final written approval (March 2006), updated based on additional written comments received till May 2006.

CONTENTS

0 OVERALL CONCLUSIONS/RESULTS OF THE RISK ASSESSMENT

CAS No. 100-97-0

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IUPAC Name Methenamine

Overall results of the risk assessment:

( ) i) There is need for further information and/or testing

(X) 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

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

Summary of conclusions:

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 releases into surface water, soil and the atmosphere. Based on the available data, methenamine represents a very low risk to the environment during all life-cycle steps considered in this report (production, processing and use).

Human Health

Workers

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

Concern is derived for skin sensitisation for all exposure scenarios. The most critical exposure scenario is scenario 2 (formulation of phenolic resin systems).

Other critical dermal toxicological endpoints are developmental toxicity and systemic toxicity after repeated contact. While for developmental toxicity concern after dermal exposure is reached for scenario 2 (formulation of phenolic resin systems), 3 (production of fuel tablets), and 4 (production of formulations used in corrosion prevention and as photo chemicals), for systemic toxicity after repeated contact conclusion iii is expressed only for the formulation of phenolic resin systems (scenario 2).

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

For the other toxicological endpoints the risk orientated conclusions result in no concern with the consequence that risk reduction measures are of low priority.

Consumers

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

Due to the skin sensitizing properties of methenamine, there is concern for the dermal exposure via cosmetic products or the use of solid fuel tablets containing methenamine.

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 all other toxicological endpoints and exposure pathways for consumers.

Man exposed indirectly 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

Combined exposure

From combined exposure at the workplace and via cosmetic products, the same conclusions apply as for workers alone for all scenarios and all toxicological endpointsHuman health risks arising from physico-chemical properties

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

1 GENERAL SUBSTANCE INFORMATION

Identification of the substance

CAS No.: 100-97-0

EINECS No.: 202-905-8

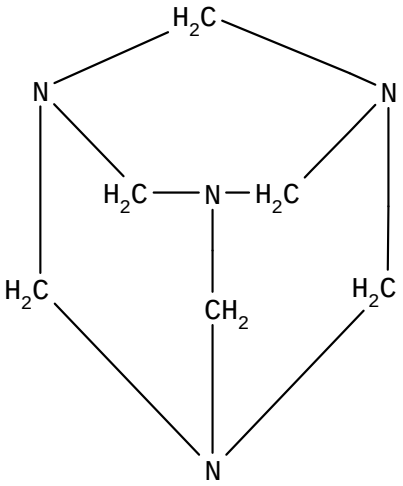
IUPAC Name: 1,3,5,7-Tetraazatricyclo-3.3.1.1$^{3.7}$-decane

Synonyma: Hexamethylenetetramine

Methenamine, Urotropin, Formin

Empirical formula: $C_6H_{12}N_4$

Structural formula:



Molecular weight: 140.2 g/mol

Purity/impurities, additives

Purity: 99 - 99.5 % w/w

Impurities: < 0.5 % water

Additives: 1.5 - 4% paraffine oil

0.5 - 3% amorphous silica

Physico-chemical properties

Physical state	at 20 °C, 1013 hPa: white crystalline powder or colorless lustrous crystals	Verschueren, 1983
Melting point	> 270 °C; from 230 °C sublimation	Heilen, G. et al., 1985
Boiling point	n.a.	
Relative density	1.331 at -5 °C	Ullmann, 1985
Vapour pressure	0.0005 hPa at 20 °C	Klipping, G., Stranski, I.N., (1958)
Surface tension	70.4 mN/m	Degussa, 1996e
Water solubility	667 g/l at 25 °C	Merck Index, 1996
Partition coefficient	- 4.15 (calculated)	Degussa, 1996f Meylan & Howard, 1995
Flash point	not determined	substance is a solid
Flammability	highly flammable [1)]	Degussa, 1980
Ignition temperature	245 °C according to Grewer	Degussa, 1980
Explosive properties	not explosive	no test conducted because of structural reasons
Oxidising properties	no oxidising properties	no test conducted because of structural reasons
Henry constant	$1.051 * 10^{-5}$ Pa * m³/mol (calculated [2)])	
Dissociation constant	8.4	INEOS Paraform, 2005

[1)] The determination of the burning level (5) and the application of UN-method class 4.1 (burn-up velocity 34.5 s/100 mm) were accepted instead of method A.10. The tests A.12 and A.13 have not been conducted for structural reasons.

[2)] The Henry law constant is based on the Water solubility-Vapour Pressure Method. Calculation models (both bond and group method) always assume an idealized form of a substance and therefore an experimental determination should be preferred. Due to the low vapour pressure an experimental Henry's Law constant is not applicable.

Classification

Current classification

The current classification and labelling to directive 67/548/EEC, 22nd ATP (Annex I, index no 612-101-00-2) is:

Classification

F, R11

R 42/43

Labelling

F, Xn

R: 11-42/43

S: (2-)16-22-24-37

Concentration Limits

None

Explanations:

F, R11	Highly flammable
Xn	Harmful
R 42/43	May cause sensitization by inhalation and skin contact.
S 16	Keep away from sources of ignition -- No smoking
S 22	Do not breathe dust
S 24	Avoid contact with the skin
S 27	Take off immediately all contaminated clothing

- (Proposal of the rapporteur)

According to the data presented below and the criteria of directive 67/548/EEC the following change of the classification according to Annex I is proposed:

Highly flammable	R 11	Highly flammable
Sensitizing	R 43	May cause sensitization by skin contact

The substance has shown skin sensitizing properties in humans. In a maximization test with guinea pigs methenamine caused strong skin sensitization.

From earlier studies a number of cases of allergic symptoms such as wheezing and asthma were reported upon exposure to methenamine. In all cases exposure to other irritant and sensitizing chemicals occurred simultaneously. The respiratory hypersensitivity could not specifically be related to methenamine exposure. From a well-documented recent study that was designed to analyse the sensitizing potential of methenamine, there was no evidence that methenamine alone may cause respiratory sensitization after occupational exposure. This study was considered to be of higher validity than the earlier reports. In consequence, there is no clear evidence of a respiratory sensitization potential of methenamine at airborne levels present at contaminated workplaces. Hence, the existing classification with R 42 „May cause sensitization by inhalation“ should be removed.

In the aqueous environment, methenamine is readily degraded by hydrolysis and biological processes. In addition to that, with EC/LC_{50}-values in an order of magnitude of g/l the substance is not toxic for aquatic organisms. Hence, no classification and labelling for environmental effects is required.

2 GENERAL INFORMATION ON EXPOSURE

2.1 PRODUCTION

The most important area of use of methenamine is the production of powdery or liquid preparations of phenolic resins and phenolic resins moulding compounds to which methenamine is added as a hardening component. These preparations are used as binders, e.g. in brake and clutch linings, abrasive products and non-woven textiles as well as in formed parts produced by moulding processes. In addition, the preparations are used as binders in formed or unformed fireproof materials employed, inter alia, in foundries and in the steel industry.

In the EU, methenamine is produced by several companies. A reliable estimation of production and use is difficult, because in the recent years some of the production sites were closed, companies were sold or merged and structures and responsibilities changed.

According to the information submitted in 1997, the total production capacity for the seven main producing sites identified in 1996 was 63,000 tonnes (SRI 1996 and specific information given by some of the producing companies). The production volume of these sites was approximately 25,000 t/a. An additional survey in 2001 was answered by only 50 % of the companies asked. However, according to the former lead company INEOS Paraform (formerly Methanova, formerly Degussa) in 2001 the following companies were main producers or importers of methenamine in the EU (EU_{15}):

Bakelite Italia S.p.A. (I)

Caldic Chemie B.V. (NL)

INEOS Paraform GmbH (formerly Degussa AG, DE)

According to information submitted by the Slovakian competent authority, an additional production site with a production of 6970 t/a in 2001 is situated in Straske –Slovakia. Although production sites in the New Member States are not formally involved in the Risk Assessment Programme of the Existing Substance Regulation, this important information was included in the risk assessment for methenamine. Hence, at least for the EU_{15} the production rates used for this assessment can be regarded as a realistic worst case.

The production capacities and production volumes updated in 2001 are listed in table 2.1.

Table 2.1 European methenamine production and capacity in 2001

Company	Capacity[t/a]	Production[t/a]
A	7,000	6,000
B	12,000	8 – 10,000
C[1]	15,000	3,800
D	unknown	7,000
total	>34,000	ca. 27,000

1: For this company only the production capacity of 1996 is available.

Some minor companies did not answer the questionnaire. For others the produced amounts are still not clear. In addition to that, the information may have changed again till finalising of this assessment report. Hence, as realistic worst case, a production volume of 30,000 tonnes is assumed for the European market (EU_{15}) and used for the exposure estimations in this report.

2.1.1 Production process

The production of methenamine can be performed according to the continuous Meissner-process in a closed system (Meissner et al. 1954; VEB Leunawerke 1987; Degussa AG 1992). The substance is obtained by the reaction of formaldehyde and ammonia in the aqueous phase under reduced pressure at approx. 40 - 90 °C.

$$6\ HCHO\ +\ 4\ NH_3\ \rightarrow\ C_6H_{12}N_4 + 6\ H_2O$$

Two other, but similar processes for the production are known. In these processes, the above reaction takes place either in the gas phase or in an inert solvent (Ullmann 1985). The three processes differ only in the technology for the isolation of the crude methenamine.

Following production, methenamine is washed, concentrated and isolated. The purified solid substance is either directly packed, coated/mixed with additives, or ground to smaller particles. The higher amount of the production is sold directly to the processing companies.

2.2 USE PATTERN

According to Degussa (1998) the main uses of methenamine were as follows:

With approximately 95 % of the total production, the main application is in the polymer and rubber industry to produce powdery or liquid preparations of phenolic resins and phenolic resins moulding compounds to which methenamine is added as curing or vulcanisation agent. The products are methenamine modified phenolic resins and phenolic resins moulding compounds (Novolake), urea formaldehyde resins and rubber.

Phenolic resins are mainly used for wooden materials and wood adhesives (30 - 35 %), moulding compounds (17 - 19 %), thermal and acoustic insulation (16 - 18 %). Furthermore they are used in coatings, laminates, foundry binders and refractories, grinding wheels and coated abrasives, brake and clutch linings, fibres, industrial filters, textile fleeces, adhesives and in formed parts.

Vulcanisation is defined as the transformation of plastic caoutchouc polymers into the rubber phase through cross-linking with energetic rays, peroxides or sulphur. The cross-linking happens in the temperature range of 120 to 160 °C. To control the rate of vulcanisation often auxiliaries like vulcanisation accelerators or inhibitors are used. In most cases the accelerators are used in combination with activators like zinc oxide or antimony sulphide.

Since methenamine belongs to the basic secondary accelerators, it is used in combination with primary accelerators like mercapto compounds in bright rubber mixtures and is processed in various kinds of caoutchoucs, e.g. natural caoutchouc, butadiene-caoutchouc, acrylnitrile-caoutchouc, acrylnitrile-butadiene-caoutchouc and styrene-butadiene-caoutchouc. The consumer products are technical rubber products, like calenders, bumpers, seals and tubing, surgical and medical products, toys and sports goods (INFU 1998).

An amount of approximately 3 % is used as chemical intermediate in nitration reactions, e.g. in the production of explosives like Hexogen and Octogen. Smaller applications include p-methylbenzaldehyd (fragance), norfenefrin (antihypotonicum), 3-formylcrotylacetat and nitrilotriacetic acid (chelating agent) (Römpp 1997; SRI 1996; US-EPA 1996).

Approximately 2 % is used as fuel tablets for camping stoves (consumer product). The tablets are produced by pressing methenamine mixed with other compound in a dry process. The product contains 95 – 97 % methenamine.

According to information submitted to the German BfR, methenamine is also used as an auxiliary ingredient in removers of limestone from coffee machines and as a preservative in cosmetics and food.

Additional uses are mentioned in the literature, but reliable data about the quantity of methenamine used in these fields are not available. Some products of minor relevance were corrosion inhibitor (metal industry), stabiliser and developer (photo industry), fertiliser, fungicide for citrus trees, urinary antiseptic, preservative in paints and for leather. Since these applications contribute < 1 % of the methenamine use in total they were not considered for the exposure estimation.

The biocidal uses of methenamine in the EU need to be evaluated under the framework of regulation 98/8/EEC. The substance was listed in Annex III of Regulation EC/2032/2003. Since no notification was submitted, the biocidal uses in the EU are only approved till 01.09.2006.

2.3 USE, PRODUCTION AND PROCESSING

According to information submitted by Bakelite (1996) and Degussa (1998), for the production of modified phenolic resins methenamine is milled and mixed at room temperature with milled phenolic resins. The mixture containing 8 - 10 % methenamine is packed in bags and big bags. These phenolic resins are sold in this uncured form as thermosetting compounds. Methenamine is used in this mixture as a curing component. The phenolic resins products are cured in production plants at temperatures between 140 and 200 C. During the polymerisation process, methenamine thermally decomposes to ammonia and formaldehyde both of which are quantitatively implemented into the resin matrix. The final thermosetting products do not contain methenamine.

For the production of modified phenolic resins moulding compounds (Bakelite 1996; Degussa 1998), milled methenamine is mixed at room temperature with milled phenolic resins and other powdery substances (wood flour, calcium carbonate, pigments etc.). The mixture containing 4 - 6 % methenamine is melted and homogenised in kneaders or roller mills at 100 to 120 °C. After cooling and milling to granules, the methenamine modified phenolic resin moulding compounds are packed in bags and big bags.

Production of methenamine modified phenolic resins moulding compounds is similar to the production of phenolic resins mentioned above.

The use pattern of methenamine according to TGD is compiled in table 2.2.

Table 2.2 Use categories of methenamine according to TGD

	Life cycle stage	**Main category (MC)**	**Industrial category (IC)**	**Use category (UC)**	**Amount [%]**
Use in phenolic resins and rubber vulcanisation	formulation and processing	Non-dispersive use **(3)**	Polymers industry **(11)**	Process regulators **(43)**	**95**
Use in nitration (explosives)	processing	Non-dispersive use **(3)**	Chemical industry: chemicals used in synthesis **(3)**	Intermediates **(33)**	**3**
Use in fuel tablets	Formulation	Non-dispersive use **(3)**	Chemical industry: chemicals used in synthesis **(3)**	Fuels **(27)**	**2**

3 ENVIRONMENT

3.1 ENVIRONMENTAL EXPOSURE

3.1.1 General discussion

3.1.2 Environmental Releases

In general, methenamine is expected to be released into the environment during production, formulation and processing via waste water and exhaust dust.

Direct releases to the soil compartment via sludge application are not expected due to the negligible sorption potential and the incineration of the sludge at the production sites.

Residual contents of methenamine in final phenolic resins and rubber products are also not expected due to complete decomposition during processing.

Since the fuel tablet are pressed in a dry process and burned without residues, no environmental releases are expected from this use.

3.1.3 Environmental fate

3.1.3.1 Degradation in the environment

3.1.3.1.1 Atmospheric degradation

In the atmosphere, methenamine is expected to be degraded by photochemical processes. The photooxidation of methenamine is estimated using the model AOPWIN with $0.87 * 10^{-10}$ cm^3 $molecules^{-1}$ sec^{-1}. Assuming a mean atmospheric concentration of $5 * 10^5$ OH-radicals/cm^3, the calculated half-life in the atmosphere is 45 min (Degussa 1996a).

Using the QSAR-model package PropertEst version 1.3 a half-life of 31 min was estimated by the rapporteur.

Since both estimations are reliable and of the same order of magnitude, the half-life of 45 minutes can be used as a worst case input for the exposure assessment at the continental and regional scale.

From the spectroscopic data available for methenamine, direct photolysis is not expected.

3.1.3.1.2 Aquatic degradation

Abiotic degradation

The kinetics of hydrolytical degradation of methenamine was studied in a pH range between 2.0 and 7.4 at 37.5 °C (Strom and Won Jun 1980). The pK_a of methenamine is 8.4. In acidic surroundings, the substance is protonated and susceptible to hydrolysis. Hence, the half-life increases with increasing of the pH. In a more basic environment the amount of protonated methenamine is decreasing and also the hydrolysis rate is. The products of hydrolytical degradation of methenamine are formaldehyde and ammonia.

The half-lives determined at 37.5°C at different pH-levels are listed in table 3.1.

Table 3.1 Hydrolytical half-lives of methenamine at 37.5 °C

pH	$t_{1/2}$ [h]
2.0	1.6
2.4	2.1
3.4	3.1
4.6	3.7
5.1	8.3
5.5	10.9
5.8	13.8
7.4	no observable degradation after 6 h

Biodegradation

Painter and King (1986) conducted a MITI (I) test where biodegradation after 28 days was approximately 47 % as determined by ThOD. DOC-elimination attained 54 % and 97 % in the two parallel vessels. No information about the pH during the study is submitted. Since hydrolysis of methenamine is highly pH-dependent it remains unclear up to which level hydrolysis might have contributed to the degradation observed in the study. The important deviation of DOC-elimination in the two assays is not useful to assess the biodegradation potential of the substance.

In a DOC Die Away Test a DOC removal of 79-108 % was observed in several assays if 30 mg/l activated sludge was used. With effluent as inoculum, lower biodegradation levels were observed (Painter and King 1986). Since no pH was documented, the degree of hydrolysis contributing to degradation remains unknown.

Van Ginkel and Stroo (1992) performed a Closed Bottle Test, into which 2 mg of activated sludge were introduced (related to dry weight) instead of 5 ml effluent/l. This does not correspond to the low inoculum concentration usually applied in the test. Considering this modification the test does not represent a screening test for ready biodegradability. The result of the test was 70 % biodegradation after 28 days.

In a ring-test performed according to the EEC Respirometry Test, the results varied considerably. In 5 out of 21 laboratories degradation achieved > 70 % related to DOC. The mean DOC-elimination was 39 % and the standard deviation 33 % (Painter and King 1985).

Biodegradation levels of 28-83 % related to ThOD and of 95-98 % related to DOC were achieved by Painter and King (1986) in another EEC Respirometry Test. The pH value was not documented.

DOC-elimination rates of 12-21 % after 3 weeks were obtained in an activated sludge simulation test (hydraulic retention time: 3 h, sludge age: 6 d) (Painter and King 1986). As the stock solutions feeding the activated sludge unit were made up weekly, a certain degree of hydrolysis has to be assumed before the stock solution enters the simulation plant.

Bodik et al. (1991) examined the elimination of methenamine in a continuous and semi-continuous pilot plant. Analysis was carried out by monitoring the test substance, no buffered medium was used. The inoculum was adapted to methenamine for 100 days. Then the effects of the age of the sludge on pH and methenamine-elimination were determined. Due to nitrification the pH value reached the acid range. With increasing age of the sludge the pH value decreased and methenamine elimination increased: at a sludge age of 10 and 50 d methenamine-elimination attained 18 % and 53 % at pH-values of 6.6 and 5.2, respectively.

Drtil et al. (1991) performed a biodegradation test of methenamine in acid medium by using a biofilm reactor. The elimination level correlated with the pH: 13 % at pH 6.6 and 44 % at pH 4.2 using a sludge retention time of 35 d.

Gomulka and Gomulka (1984) did not observe oxygen consumption after 17 days at a concentration of 2 and 4 mg methenamine/l. No method was reported.

Swope and Kenna (1950) obtained a BOD of approximately 2 % of ThOD after 5 days at pH = 7. The performance of the test was insufficiently documented.

3.1.3.1.3 Degradation in soil

No information about degradation of methenamine in soil is available.

According to production, processing, and uses identified, releases of methenamine to the soil compartment can be excluded. Since methenamine does not adsorb to sewage sludge to a significant extent, exposure of agricultural soil via sludge application is considered to be negligible, too. A relevant exposure of soil by atmospheric deposition can also be excluded, because methenamine is degraded quickly in the air and transport via air is unlikely. Further information on degradation in soil is not required.

3.1.3.1.4 Summary of environmental degradation

In the atmosphere, methenamine is expected to be degraded by photochemical processes with a half life of < 1 hour.

In aqueous systems, methenamine is susceptible to hydrolysis. The process is strongly pH-depending. At acidic pH-levels the substance is degraded in a few hours, at neutral and basic

pH-levels the half life increases to several days. For environmental relevant conditions, hydrolytical degradation can last several days – weeks, e.g. in surface water with pH > 7.

The available tests on biodegradation delivered different results. In standard screening tests on ready biodegradation, degradation levels between 28 % and > 100 % were determined. In sewage treatment plant simulation studies the elimination rate was between 12 % and 53 %, depending on the test conditions e.g. the aging of the sludge. These differences might also be explained by the susceptibility to hydrolysis at different pH-levels, because hydrolysis is expected to be the decisive step also in the available biodegradation tests. In addition, the rate biological degradation might depend on the amount of protonated methenamine. At acidic pH-levels, most of the substance is protonated while in a more basic environment the amount of protonated methenamine is decreasing. The neutral molecule could be more bioavailable and therefore subject to microbial degradation.

Taking these findings together, hydrolysis seems to be the major degradation pathway for methenamine in the environment. At acidic pH-levels, methenamine is quickly degraded hydrolytically. At neutral and basic pH, the rate of hydrolysis decreases, and degradation might be supported by microbial activity.

However, a continued, long-term exposure of aqueous systems to methenamine cannot be excluded completely. This needs to be considered when assessing the risks for aquatic organisms. In addition to that, the products of degradation, formaldehyde and ammonia also need to be considered for the risk assessment, especially of assessing the risk for acidic water bodies.

No information about degradation of methenamine in soil is available. Since releases of methenamine into the soil compartment can be excluded, further information is not required.

For the risk assessment the following aspects were considered:

In the sewage treatment plant, assuming a neutral pH and a hydraulic retention time of a few hours, only a minor fraction of methenamine is expected to degrade hydrolytically.

This is confirmed by the activated sludge simulation test (Painter and King, 1986) and the simulation study (Bodik et al. 1991): Using sludge aged for 50 days in a pilot plant, Bodik et al. (1991) observed a degradation of approximately 50 %. Using sludge aged for 10 days the degradation was only 18 %. Since a mean sludge age in a WWTP of 9.2 days is proposed by the TGD, the degradation in a sewage treatment plant might be of minor relevance.

In addition to that, the elimination in a waste water treatment plant was calculated using the model SIMPLETREAT 3.0. Assuming a log H of -4.98, a log K_{OW} of -4.15 and no biodegradation of methenamine as a realistic worst case, the substance was neither adsorbed nor degraded or removed, but completely directed to water. This calculation complies with measured data from aerated municipal sewage treatments (Gomulka and Gomulka 1984).

After the release of the remaining substance from the waste water treatment plant into surface water, methenamine is expected to be further degraded hydrolytically to ammonia and formaldehyde. This needs to be considered especially for acidic receiving waters. Formaldehyde is classified as readily biodegradable (OECD 2002), and hence expected to be degraded by microbial activity. Ammonia is natural widely occurring, e.g. as excretion

product of aquatic organisms. Ammonia is expected to volatilise from water to a certain degree. Under aerobic conditions it is transformed by nitrifying bacteria to nitrite and nitrate.

As a realistic worst case for the degradation of methenamine a hydrolytical half-life of ~ 10 days is assumed. The half-life for the biodegradation of the hydrolysis products is estimated to be 15 days (according to the TGD). Hence, as realistic worst-case a half-life of 15 days, corresponding degradation rate constant of **0.046 d^{-1}** is used for the exposure estimation.

3.1.3.2 Distribution

Methenamine is highly water soluble in water (667 g/l) and soluble in alcohol and chloroform. In organic solvents the substance is insoluble. The calculated log K_{OW} is -4.15 (Degussa 1996).

The vapour pressure of methenamine is 0.05 Pa at 20 °C. The Henry's law constant of 1.051 * 10^{-5} Pa * m³/mol, calculated from the physical chemical properties as presented in Chapter 1, indicates that the substance is non-volatile from aqueous solutions (Lyman et al. 1982). Degussa (1986) estimated a Henry's law constant of 8.02 * 10^{-6} Pa * m³/mol assuming a water solubility of 874 g/l. However, since this solubility is not reliable, the Henry's law constant of 1.051 * 10^{-5} Pa * m³/mol (log H = -4.98) is used in the exposure estimation.

The adsorption and desorption behaviour of methenamine was not determined. A calculated K_{OC} of 54.7 l/kg using the QSAR-model PCKOCWIN version 1.57 was submitted by Degussa (1996). According to the TGD (chapter 4, table 4, nonhydrophobics) a K_{OC} of 0.073 l/kg was calculated assuming the log K_{OW} of -4.15. Since this K_{OW} seems to be more reliable than the assumptions used as input for the QSAR-model, this value is used for further calculations.

Using a K_{OC} of 0.073 l/kg, the partition coefficients in different compartments can be estimated using the default organic carbon contents as proposed in Table 3 of Chapter 3 of the Technical Guidance Document. The calculated partitioning is depicted in table 3.2.

Table 3.2 Partitioning coefficients of methenamine

Parameter	organic carbon content [%]	partition coefficient [l/kg]
Kp (soil - water)	2	< 0.01
Kp (sediment - water)	10	< 0.01
Kp (suspended matter - water)	10	< 0.01
Kp (raw sewage - water)	30	0.02
Kp (activated sludge - water)	37	0.03

Based on the physical chemical properties of methenamine the hydrosphere is the most likely target compartment in the environment. This is supported by an estimation of the theoretical steady-state distribution between the environmental compartments according to the Mackay fugacity „Environmental Quality Criterion" (EQC)-model (level 1) where a distribution of

nearly 100 % into the aqueous phase was calculated while the distribution into air, soil, sediment, suspended matter and biota remain below 0.001 %.

These results were comfirmed by the calculation using the model SIMPLETREAT 3.0 mentioned before, where methenamine was completely directed to water.

3.1.3.3 Accumulation

The estimated Koc of 0.073 l/kg indicates no potential for geoaccumulation. Methenamine is mobile in soil. If relevant amounts reach the soil, the substance might leach into the groundwater.

No studies on the bioaccumulation of methenamine are available. Walton and Davis (1980) presented a measured log Kow of -2.18. The calculated log Kow is -4.15 (Degussa 1996). However, neither of the Kow values indicates a potential for bioaccumulation. Hence, no further information concerning bioconcentration or bioaccumulation is required.

3.1.4 Exposure of the aquatic compartment (incl. sediment)

The information describing releases from production and processing of methenamine into the aquatic environment is incomplete. No reliable data on actual production and emissions were submitted from some of the companies which might be relevant. The available information originates from 1996 and partly from 2001. Specific data are only available for some of the production sites. Therefore, several worst-case assumptions were integrated in the exposure assessment.

The ecotoxicological information available for methenamine indicates that the hazard potential of the substance is low. Taking this and the low reliability of the information about releases into aqueous systems into account, no site specific concentrations were calculated. Instead, it was decided to estimate the emissions into surface water using the generic exposure scenarios for releases during production and processing described in the Technical Guidance Document as a realistic worst case.

3.1.4.1 Calculation of predicted environmental concentrations (PEC_{local})

3.1.4.1.1 Estimation of $Clocal_{water}$ following production

Since no details are available for every production site, the maximum production volume of 10,000 t/a (company B) from the indicated ranges is used to estimate the local PECs.

The Clocal for this production volume is estimated using the default values according to the TGD. Since for methenamine the target compartment is the aqueous phase, the fraction is assumed to be directed completely to water. The respective default emission factor is 0.3 %, and the fraction of main source 1.0. The emission is distributed to 300 days. In addition to

that, a effluent discharge-rate of the waste water treatment plant of 10,000 m^3/day, and a dilution of 1:40 is assumed.

processing volume:	10,000 t/a
emission factor:	0.003 (table A 1.1)
fraction of main source:	1.0 (table B 1.3)
duration of emission:	300 d (table B 1.3)
fraction directed to water:	1
flow-rate wwtp:	10,000 m^3/d
dilution factor:	1:40

Using these input data as realistic worst-case assumption, a $Clocal_{water}$ of 0.25 mg/l is estimated.

3.1.4.1.2 Estimation of $Clocal_{water}$ following processing as intermediate

A maximum amount of 3 % of methenamine produced (900 t/a) is sold as intermediate for explosives, p-methylbenzaldehyd, norfenefrin, 3-formylcrotylacetat, nitrilotriacetic acid and pharmaceuticals. As no further details are available, the Clocal is estimated using the A- and B-tables from the Technical Guidance Document. The following input data were assumed:

processing volume:	900 t/a
emission factor:	0.02 (table A 3.3)
fraction of main source:	0.4 (table B 3.2)
duration of emission:	90 d (table B 3.2)
fraction directed to water:	1
flow-rate wwtp:	2,000 m^3/d
dilution factor:	1:40

Using these input data as realistic worst-case assumption, a $Clocal_{water}$ of 1.0 mg/l is estimated.

3.1.4.1.3 Estimation of $Clocal_{water}$ following formulation of phenolic resins/rubber mixtures

Methenamine is used as curing agent for phenolic resins, phenolic resins moulding compounds and urea resins. According to specific information (Bakelite 1996), the uncured phenolic resins consist 8 - 10 % methenamine and the uncured phenolic resin moulding compounds 4 - 6 %. No information about the formulation of urea resins is available.

According to Stanford Research Institute (1996) in the EU phenolic resins were manufactured in approximately 70 companies and urea resins were produced in 56 companies.

The other main application is as vulcanisation accelerator. No information is available about the quantity of methenamine used for this process and the number of processing sites.

The total production volume of methenamine in the EU is assumed to be 30,000 t/a. Aproximately 5 % are employed as intermediates and for the production of fuel tablets. The remaining 95 % - 28,500 t/a - are used to formulate phenolic and urea resins, and as accelerators.

The maximum percentage of methenamine in the resins is 10 % (see before) and the total tonnage assumed for this uses in the EU is 28,500 t/a. To choose the appropriate TGD-scenarios for the exposure estimation, the maximum tonnage of products containing methenamine is needed, which is estimated to be 285,000 t/a.

Exposure is calculated as follows:

formulation volume:	285,000 t/a
product volume:	28,500 t/a
emission factor:	0.003 (table A 2.1)
fraction of main source:	0.4 (table B 2.9)
duration of emission:	300 d (table B 2.9)
fraction directed to water:	1
effluent flow:	10,000 m^3/d
dilution factor:	40

Using these input data as worst-case assumption, a $Clocal_{water}$ of 0.3 mg/l is estimated.

This estimation can be considered as a worst-case for the formulation of phenolic resins, urea resins and the use as accelerator. Hence, for these uses no further calculations are required.

3.1.4.1.4 Estimation of $Clocal_{water}$ following processing in polymer industry

As for the formulation of phenolic resins, no reliable information exists for the processing step. Hence, for this process also a volume of 28,500 t/a (product) is assumed as worst case.

The mixtures of methenamine and phenolic resins are cured at temperatures between 140 and 200 °C. During the polymerisation process methenamine is decomposed thermally to ammonia and formaldehyde which are both quantitatively incorporated into the resin matrix. The final thermosetting products do not contain any methenamine. However, according to the TGD the emission is estimated as follows:

processing volume: 285,000 t/a

product volume: 28,500 t/a

emission factor: 0.00005 (table A 3.11)

fraction of main source: 0.05 (table B 3.9)

duration of emission: 300 d (table B 3.9)

fraction directed to water: 1

effluent flow: 10,000 m^3/d

dilution factor: 40

Using this input data as a realistic worst-case assumption, a $Clocal_{water}$ of 6 x 10^{-4} mg/l is estimated.

No further emissions of methenamine are expected after polymerisation is completed.

3.1.4.2 Measured levels

Since methenamine is considered as a substance of low environmental concerns, only minor information from monitoring projects exists. Hence, the data should only be treated as indicative values.

In a Swedish project, effluents of three large sewage treatments plants were analysed for organic pollutants by GC-MS. In 1993, methenamine could be detected in a concentration of 0.5 µg/l in the effluent of the Malmö sewage treatment plant. Since the effluents from the Malmö sewage treatment plant are discharged into the Öresund., the rubber industry in that area might be the source of methenamine. In effluents of the sewage treatment plants in Stockholm and Göteborg no methenamine could be detected (Paxéus 1996).

At production site A, a concentration of approximately 0.1 mg/l was determined in the waste water after biological treatment.

In a monitoring project at a former production site in UK with a capacity of 7,000 t/a, methenamine was monitored directly in the sewage plant, and in the receiving river

downstream of the emission source. The 90 percentile of the measurements in 1.2 km distance was 1 mg/l, and 5 km downstream 0.4 mg/l. However, this site was closed and deconstructed in 2000.

Table 3.3 Monitored concentrations of methenamine in aquatic compartment

Site	concentration [mg/l]	corresponding to	Remarks
A	~0.1	$Clocal_{water}$	production site, concentration in waste water after biological treatment
UK, site closed	15	$Clocal_{eff}$	production site, concentration in sewage treatment plant; 90-percentile of readings
	1	$Clocal_{water}$	concentration in receiving river ca. 1.2 km from emission source; 90-percentile of readings
	0.4	$Clocal_{water}$	concentration in receiving river ca. 5 km from emission source; 90-percentile of readings
SE, Malmö	$0.5*10^{-3}$	$Clocal_{eff}$	effluent of municipal waste water treatment plant processing site (rubber industry)

3.1.4.3 Comparison between predicted and measured levels

The monitoring projects confirm at least that methenamine is not degraded completely in wastewater treatment plants.

The local concentration predicted for a production site with 10,000 t/a and a industrial treatment plant as described in chapter 3.1.4.1 (0.25 mg/l) is between the concentrations monitored in the effluents of the treatment plant of site A (production volume 6,000 t/a) and the concentration measured in the river below the former site in UK (production volume 7,000 t/a). The monitoring data are useful to confirm the assumptions and the estimated local concentrations as realistic.

3.1.4.4 Sediment

According to the physico-chemical properties methenamine is not expected to be distributed into sediment in relevant amounts. Taking into additional account the findings of the ecotoxicological tests using aquatic organisms (non toxic), a risk for this compartment can be excluded. An estimation of the exposure for this compartment is therefore dispensable.

3.1.5 Atmosphere

Due to the vapour pressure of methenamine (0.05 Pa) a release into air cannot be completely excluded. However, the Henry-coefficient is low and no distribution from water into air is to anticipate. In addition to that, with a estimated half-life < 1 hour the substance is expected to

degrade quickly in air. It can be assumed that the major degradation products are formaldehyde and ammonia.

The available information indicate that methenamine shows no potential for air contamination and for long-range transport via air. Hence, a prediction of concentrations for the compartment air is not necessary.

3.1.6 Terrestrial compartment

According to the uses identified, direct releases of methenamine to the soil compartment can be excluded. An input via sludge application on agricultural soil is considered to be negligible, too, as methenamine does not adsorb to the sewage sludge to a significant extent. Consequently, an exposure of soil only might occur by atmospheric deposition. As argued in section 3.1.5 the substance is degraded quickly in the air and transport via air is unlikely. Hence, this pathway of exposuring the terrestrial compartment is negligible, too.

3.1.7 Non compartment specific exposure relevant to the food chain

It is not required to carry out a risk characterisation for secondary poisoning since there is no indication of methenamine possessing a bioaccumulation potential.

3.1.8 Continental and regional concentrations

It is assumed that the substance is mainly released into the aquatic compartment. The total release is estimated assuming that the waste water is treated in an appropriate plant at all production sites.

As a realistic worst case, the complete EU production volume of 30,000 t/a and an emission factor of 0.003 according to TGD (according to ESD or A- and B- table) are used to calculate the release into aqueous systems from waste water treatment at the production sites. In addition to that, releases from industrial processing and formulation of methenamine were calculated according to the default values of the TGD and depicted in table 3.5. Since the formulation of fuel tablets is a dry process (pressing), no releases were considered from this use. Assuming that the substance is completely degraded in the curing process, diffuse releases from residual methenamine in final resin or rubber products are not to expect.

A default connection rate of 80 % to biological waste treatment plants is assumed (table 3.6). The continental background concentration is estimated by summarising the emissions of production, processing and formulation. To estimate a regional background concentration, emissions of a worst-case site with a production of 10,000 t/a are compared to emissions estimated according to the EU-standard regional model with 10 % of the regional releases. Accordingly, as a realistic worst-case assumption, the highest value from the two approaches will be chosen; i.e., a single production site using 10,000 t/a is used to calculate the regional background concentration. This results in regional releases of 30 t/a into surface water via stp. The PECregional and PECcontinental are calculated using the model SIMPLEBOX version 2.0a. The input-parameters are listed in Appendix A, the results are listed in table 3.7.

Table 3.4 Direct and indirect releases to the aquatic compartment

application	volume [t/a]	emission factor	release [t/a]	release via wwtp [t/a]	direct release [t/a]
Production	30,000	0.003	90	90	0
processing as intermediate	900	0.02	18.0	14.4	3.6
formulation of resin and rubber mixtures	28,500	0.003	85.5	68.4	17.1
processing in polymer industry	28,500	0.00005	1.4	1.1	0.3
Sum			**195**	**174**	**21**

Table 3.5 Input data for background concentration

compartment	total [t/a]	continental [t/a]	regional [t/a]
water (direct)	21	19	-0
water (via wwtp)	174	157	30

Table 3.6 PECregional calculated for methenamine

$PECregional_{water}$: $3.3 * 10^{-4}$ mg/l

$PECcontinental_{water}$: $2.9 * 10^{-5}$ mg/l

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

3.2.1 Aquatic compartment

In addition to the data reported for methenamine, information about the effects of the products of hydrolytic degradation, formaldehyde and ammonia is included. The test results for formaldehyde were taken from the OECD SIAR (OECD 2002) without further validation. The data inserted for ammonia were taken without further review from the US-EPA database aquire and the US EPA Aquatic Life Ambient Water Quality Criteria for Ammonia document (US EPA 1999). It needs to be emphasised that this additional information is only of indicative value. It is included in the draft report to deliver an indication about possible effects of the metabolites.

3.2.1.1 Toxicity to fish

According to the available information, methenamin is not toxic for fish following short-term exposure. Walton and Davis (1980) examined the impact of 30 and 60 g methenamine/l on *Cyprinodon variegatus*. The static test was conducted in brackish water (salinity 20.5 ‰, pH 7.7, alkalinity 174 mg/l as $CaCO_3$). A (nominal) 96 h LC_{50} of 49 g/l was reported.

A flow-through test with juveniles of *Pimephales promelas* (aged 33 d) was carried out in lake water (pH 7.8, hardness 44.9 mg/l as $CaCO_3$). The LC_{50} (96 h) based on measured concentrations was 49.8 g/l (Geiger et al. 1988).

Dupont de Nemours (1976) determined a (nominal) 96 h LC_{50} of 41 g/l for *Lepomis macrochirus*.

Juveniles of *Alburnus alburnus* collected in the field were exposed by Lindén et al. (1979) in a static test run with filtered brackish water (salinity 7 ‰, alkalinity 75 mg/l as $CaCO_3$, temperature 10°C) applying a method developed by Bengtsson (1978). The non-adjusted pH of 7.8 remained "close to constant" throughout the test. A (nominal) 96 h LC_{50} of > 10 g/l was determined.

The main metabolite from hydrolytical degradation of methenamine is formaldehyde. According to the SIDS Initial Assessment Report (OECD 2002) the acute toxicity of formaldehyde to fish (LC_{50}, 96 h) was determined between 6.7 and 1,020 mg/l. The most sensitive species tested are *Morone saxatilis* (marine, LC_{50}, 96 h: 6.7 mg/l), and *Ictalurus melas* (freshwater, LC_{50}, 96 h: 24.8 mg/l.

The other degradation product, ammonia is also toxic to fish. To give an indication about the acute toxicity, the US-EPA aquire database was screened for data without further validation or quality assurance. The LC_{50} values (96 h) available were in the magnitude of 0.1 to 2 mg/l. The differences are contributed to diverse species and test conditions. In long-term studies including different life stages, the lowest NOEC was approximately 0.02 mg/l.

3.2.1.2 Toxicity to invertebrates

Walton and Davis (1980) exposed *Daphnia magna* to methenamine dissolved in reconstituted water (pH 7.8, alkalinity 114 mg/l as $CaCO_3$). They reported a 24 h LC_{50} of 44 g/l and a 48 h LC_{50} of 36 g/l.

Lindén et al. (1979) examined the susceptibility of adult *Nitocra spinipes*, a harpacticoid crustacean, in a static test conducted with filtered brackish water (salinitiy 7 ‰, pH 7.8, alkalinity 75 mg/l as $CaCO_3$). A 96 h LC_{50} of 92 g/l was determined.

For aquatic invertebrates the metabolite formaldehyde is also more than one order of magnitude more toxic than methenamine. According to the SIDS Initial Assessment Report (OECD 2002) in acute tests using aquatic invertebrates EC_{50} values were between 0.46 – 1,800 mg/l. For *Daphnia pulex* an EC_{50} (48 h) value of 5.8 mg/l was determined.

For ammonia, the available EC_{50} values (48 h) determined in acute tests using freshwater invertebrates range between 0.2 and 5 mg/l. In long-term studies, the lowest NOEC values were approximately 0.1 mg/l.

3.2.1.3 Toxicity to algae

Selenastrum capricornutum was exposed in a 14 d growth inhibition test following U.S. EPA (AAP: BT) guidelines. Bold's mineral salts medium was slightly modified by adding tris buffer and $NaHCO_3$ and an illumination regime of 12 h light/12 h dark was applied. The pH of the medium was 7.5. The maximum specific growth rates for 1, 2.5 and 5 g methenamine/l (dosed as flo-powder) were determined on the basis of cell counts (initial algal concentration approximately 10^3 cells/ml).

A value of 1.5 g/l was estimated as concentration not resulting in a significant growth rate reduction. Here, the rising impact of turbidity on the results with increasing methenamine concentrations was taken into account, although this impact is not exactly quantifiable. Hence, the test is formally not valide. However, taking the findings of the other tests into account, the result seems to be reliable and conservative enough for a risk assessment. The 14 d $E_rC^1{}_{50}$ estimated from the growth curves is 3 g/l (Walton and Davis 1980).

In a cell multiplication inhibition test using the green algae *Scenedesmus quadricauda* formaldehyde was one order of magnitude more toxic than methenamine itself. During this 8 day test effects on growth rate were observed after 24 hours at 0.3 mg/l. A toxic threshold of 0.88 mg/L was defined (OECD 2002) A standard test using *Scenedesmus quadricauda* delivered a 24h-EC_{50} of 14.7 mg/l indicating that algae are more susceptible to formaldehyde than to methenamine, too.

The toxicity of ammonia for different species of green algae (EC_{50}, 72- 120 h) is in the magnitude of 1- 10 mg/l. Compared to fish and aquatic invertebrates, the lower toxicity of ammonia for algae might be contributed to the fact that most algae species are able to use ammonia as nitrogen source.

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[1] E_rC ist the effective concentration with regard to the endpoint growth rate of the algae population

3.2.1.4 Toxicity to microorganisms

Only one test with microorganisms is available that can be used for the risk assessment. Hockenbury and Grady (1977) tested the inhibition of nitrification by methenamine. 100 mg/l, the highest concentration tested, did not reveal any effects for a test duration of 2 hours. The test was conducted at pH 8.1.

The other available studies using aquatic microorganisms are not useful to derive a PNEC and to assess the risk for waste water treatment plants, because the tests were conducted with specific species not relevant for a wwtp or the test results could not be validated due to missing information on test conditions.

3.2.1.5 Summary

The available ecotoxicological studies indicate that methenamine itself is non-toxic for aquatic organisms, at least following short term exposure. It might be assumed that the main hydrolysis product, formaldehyde, would contribute to the effects determined in these tests. However, the effects observed in the tests were related to methenamine , because they were conducted at pH > 7 where hydrolysis to formaldehyde is mostly prevented.

In addition to the tests using standard organisms, some supplementary test results were reported by Denzer (1961) for slightly acidic conditions. The studies are not valid due to insufficient descriptions of the test procedure. However, since very soft natural test water was used in the studies (pH usually < 7, temperature 18°C) and similar effects on motility were observed, the results are useful as additional information and might give an indication about pH-effects on toxicity. The threshold concentrations determined were 5 g/l for rainbow trout, 8 g/l for *Gammarus sp.* and 6.5 g/l for larval mayflies (*Epeorus assimilis*). Considering the increased hydrolysis rate of methenamine at low pH-levels, these data may be interpreted as a hint for additional effects of the acutely more toxic metabolite formaldehyde. However, the results are still in a g/l range indicating that the substance is non-toxic for aquatic organisms.

When reaching the aqueous environment, methenamine is degraded hydrolytically to ammonium and formaldehyde. The rate of hydrolysis is strongly pH-dependent. While the substance is degraded rapidly at acidic pHs, it seems to be more stable to hydrolysis at pHs > 7 and may persist in the water phase for several days, before being degraded biologically. Since this effect might occur under environmental relevant conditions, a long term exposure of aquatic systems and organisms cannot be excluded completely. No studies are available concerning the long-term effects on fish and invertebrates. However, before asking for additional information, the following aspects need to be considered:

- methenamine was shown to be biodegradable
- methenamine was non-toxic in the available tests using aquatic organism
- one degradation product, formaldehyde, is ready biodegradable, the other degradation product, ammonia, is a naturally occurring substance known for many metabolic

pathways in organisms. The environmental levels of both due to degradation of methenamine are very low compared to releases from other sources.

Taking these findings together, a long-term exposure of aquatic organisms to ecotoxicological relevant concentrations of methenamine can be excluded. Hence, further information concerning long-term effects on aquatic organisms is dispensable.

Hydrolysis was also identified as main degradation pathway in the studies on biological degradation. The products of the hydrolytical degradation are formaldehyde and ammonia. The ecotoxicological information available for formaldehyde (OECD 2002) shows that at least following short-term exposure fish, invertebrates and algae were more than three orders of magnitude more susceptible to this metabolite than to methenamine itself. However, formaldehyde is readily biodegradable and volatile. Therefore it is not expected to persist in the aqueous phase and long-term exposure of aquatic organisms to this substance can be excluded, too.

In addition to that, it needs to be emphasised that formaldehyde itself is produced with 5–6 millions t/a. The production of methenamine is aproximately 30.000 t/a at 4 sites in Europe (EU_{25}). If it was assumed that the complete production of methenamine might be transformed into formaldehyde, this contribution would be < 1% of the European formaldehyde production. Hence, the environmental levels of formaldehyde due to the degradation of methenamine are very low. Regarding the effects on the environment formaldehyde was identified by the OECD SIAR as “candidate for further work” (OECD 2002). Hence, the risks of formaldehyde need to be addressed taking into account the complete situation for this substance.

The other degradation product is ammonia. At least for fish and aquatic invertebrates, ammonia is also more toxic than methenamine. Ammonia is natural widely occurring, e.g. as excretion product of aquatic organisms. In addition, ammonia is a degradation product of several substances. The environmental levels of ammonia due to degradation of methenamine are very low. From the water-phase, ammonia is expected to volatilise into air to a certain degree. Under aerobic conditions it is transformed by nitrifying bacteria to nitrite and nitrate. Taking these facts into consideration, it is also preferred to assess the risks of ammonia in a separate risk assessment addressing the complete situation for this substance.

According to its physico-chemical properties methenamine is not expected to be distributed into sediment. Hence, no information on effects on sediment –dwelling organisms is needed and the risk for this compartment is considered to be low.

3.2.1.6 $PNEC_{WATER}$ calculation

Since long-term effect values for fish and invertebrates are lacking, the lowest available EC/LC 50 value (3 g/l for algae) is used for the derivation of a provisional PNEC according to the TGD, supplemented by a factor of 1000:

$PNEC_{water}$ = 3 mg/l

3.2.1.7 Sediment

Results of sediment tests are not available. However, in view of the irrelevant adsorption of methenamine to sediment it can be assumed that in such tests the exposure through sediment pore water does not differ significantly from that to methenamine in the overlaying water and that hazards resulting from uptake of sediment can be excluded. The same holds for the toxic metabolites of slow methenamine degradation. Therefore, the derivation of a $PNEC_{sediment}$ is not necessary.

3.2.1.8 $PNEC_{wwtp}$ calculation

Although most of the available data cannot be used for a $PNEC_{wwtp}$ derivation they indicate that no toxicity of methenamine on microorganisms occurred under neutral and basic conditions. A tentative $PNEC_{wwtp}$ may be derived based on the NOEC of 100 mg/l found for nitrifying bacteria. According to the TGD an assessment factor of 1 has to be applied. Therefore:

$PNEC_{wwtp}$ = 100 mg/l

3.2.2 Terrestrial compartment

Reliable data about the effects on terrestrial organisms are not available. However, no relevant exposure of the terrestrial compartment is to expect. In addition to that the available information indicate that the substance is non-toxic and of low environmental concern. Hence, the risk for terrestrial organisms is considered to be low.

3.2.3 Non compartment specific effects relevant to the food chain

According to its physico-chemical properties and the model calculations on lipophilicity, a bioaccumulation potential for methenamine can be excluded. Therefore, an effect assessment for secondary poisoning is not required.

3.3 RISK CHARACTERISATION

3.3.1 Aquatic compartment

A $PNEC_{water}$ value of 3 mg/l was derived in the aquatic effects assessment. The PEC/PNEC ratios for relevant areas identified (production, formulation, processing) are listed in table 3.8.

Since not for all sites actual data exist, a site producing 10,000 t/a as represented by company B is taken as a realistic worst case example. To characterise the risk following production, the volume released by this site and the C_{local} as determined in chapter 3.1.4.1. was taken into account. The estimated C_{local} is 0.25 mg/l. Adding a background concentration of 0.00033 mg/l as calculated in chapter 3.1.8., the resulting PEC_{local} for this realistic worst-case production site is 0.25 mg/l. Using this concentration and the PNEC of 3 mg/l mentioned above, the risk can be characterised by the following PEC/PNEC ratio:

0.25 / 3.0 = 0.08

indicating a very low risk for the receiving surface water assuming this worst-case situation. Considering the ratio between predicted concentration for aqueous systems (PEC) and the concentration that might be harmful for aquatic organisms, no risk for aquatic ecosystems is expected. A site specific risk assessment for production is not required even for much higher production levels.

Table 3.7 PEC/PNEC ratios for the aquatic compartment

Process	Data	Scenario	PEC_{local} (mg/l)	PEC/PNEC
Production	generic	site B	0.25	0.08
Processing	generic	intermediate	1.0	0.3
Formulation	generic	Phenolic resins/rubber mixtures	0.3	0.1
Processing	generic	polymer industry	0.0009	< 0.001

Considering these worst-case assumptions using generic (default) data, it can be concluded that the risk for aquatic ecosystems is very low and no further information and/or testing is needed.

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

Since the hydrolytical degradation products, formaldehyde and ammonia, are acutely more toxic for aquatic organisms, especially for acidic waters additional hazard might occur from these degradation products. However, formaldehyde is produced with 5–6 millions t/a, and ammonia is natural widely occurring. The contribution to the environmental levels due to degradation of methenamine are very low for both, formaldehyde and ammonia. In addition,

both are degradable and volatile to a certain degree. Taking these into account, it is preferred to address the situation for formaldehyde and ammonia in separate risk assessments considering all possible releases into the environment.

3.3.2 Atmosphere

Considering the vapour-pressure of methenamine, the Henry-coefficient and further physico chemical properties of the substance, the rate emitted into air during synthesis, processing and formulation will be very low. The target compartment of the substance is the aqueous phase. Taking into additional consideration the atmospheric half-life of < 1 hour, a quick degradation to formaldehyde and ammonia is expected once the substance is emitted into air.

The available information indicate that methenamine shows no potential for air contamination and for long-range transport via air. Hence, it can be concluded for all uses considered here, that the risk for the compartment air is low and no further information and/or testing is needed.

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

No information concerning effects on terrestrial ecosystems or surrogate species from terrestrial biocenosis is available. A quantitative risk characterisation is not possible.

According to the available information about production and processing of methenamine, and the uses identified, direct releases of methenamine to the terrestrial compartment can be excluded. An input via sludge application on agricultural soil is considered to be negligible, too, as methenamine does not adsorb to the sewage sludge to a significant extent. Consequently, an exposure of soil only might occur by atmospheric deposition. As argued in capter 3.1.5 the substance is degraded quickly in the air and transport via air is unlikely. Hence, this pathway of exposing the terrestrial compartment is negligible, too.

It can be concluded for all uses considered here, that the risk for the terrestrial compartment is low and no further information and/or testing is needed.

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

Taking into account the data on adsorption, lipophilicity and bioconcentration potential, no indication of methenamine showing a bioaccumulation potential exists. Hence, it is not required to carry out a risk characterisation for secondary poisoning.

It can be concluded for all uses considered here, that the risk for the food chain is low and no further information and/or testing is needed.

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

3.3.5 PBT Assessment

The available information is sufficient for a pbt assessment.

The studies on abiotic and biological degradation indicate that methenamine is hydrolytically instable especially at low pH values and to a certain degree biodegradable. Hence, it cannot be decided whether the screening-criteria for persistence (not readily biodegradable) is met. However, the available information is reliable to decide that methenamine is not persistent in the environment. In addition to that, the substance is not adsorptive and not expected to be distributed into sediment where is may resist to degradation processes.

The $logK_{OW}$ calculated is -4.2 indicating no potential for bioaccumulation ($logK_{OW} < 4.5$).

No information concerning long-term effects is available. In the acute tests methenamine was non-toxic for aquatic organisms. Taking the information about degradability and acute effects on aquatic organisms together, for methenamine long term toxicity (e.g. NOEC < 0.01 mg/l) can be excluded.

Taking these findings together, methenamine does not exhibit any pbt- or vpvb properties and hence, is not a pbt or vpvb candidate.

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

Methenamine is mainly produced by 4 different companies in the EU with a total production capacity of 39,000 t per year. The production volume in 2001 amounts to approx. 30,000 t.

The most important area of use of methenamine is the production of powdery or liquid preparations of phenolic resins and phenolic resins moulding compounds to which methenamine is added as a hardening component. These preparations are used as binders, e.g. in brake and clutch linings, abrasive products and non-woven textiles as well as in formed parts produced by moulding processes. In addition, the preparations are used as binders in formed or unformed fireproof materials employed, inter alia, in foundries and in the steel industry.

A use pattern is given in Degussa (1998):

95 % crosslinking agent in phenolic resins and phenolic resins moulding compounds, uses in urea-formaldehyde resins and in rubber

3% chemical intermediate in nitration reactions (e.g. production of explosives)

2 % production of fuel tablets (the proportion of the substance amounts to 97 %).

Further areas of use are corrosion inhibition and uses in photochemicals (Roempp, 1997). Of minor importance are uses in paints and lacquers as well as in the preservation of foods (Ullmann, 1995).

The Swedish product register gives 3 products for use in the consumer area out of a total of 84 products.

According to reports given from German industry to the BfR, it is also used as an auxiliary ingredient in removers of limestone from coffeemachines. Methenamine is used in the pure form in solid fuels e.g. for camping stoves (information of the reporting company).

Methenamine is also used as a preservative in cosmetics.

Methenamine is used in human medicine to treat urinary tract infections.

4.1.1.2 Occupational exposure

The occupational exposure limit in Sweden and Norway amounts to 3 mg/m^3 (TLV, Ariel, 1999). OELs do not exist in the other EU member states or in the USA.

Industrial activities using methenamine present opportunities for exposure. Exposure ranges depend on the particular operation and the risk reduction measures in use. Due to the physico-chemical properties of the substance (solid at room temperature, vapour pressure 0.05 Pa) inhalation and dermal exposure to dusts during the handling of the powdery substance or powdery preparations are expected to be the main source of exposure.

Methenamine is a colourless, crystalline substance which decomposes under the effect of heat (decomposition temperature 200 °C). Low-dust, pourable powders are obtained by addition of paraffin.

The phenolic resins and phenolic resins moulding compounds are heated for the purpose of hardening. In this, the possibility cannot be excluded that, in addition to the thermal decomposition of methenamine, the substance itself may also be released and leads to inhalation exposure.

Relevant occupational exposure scenarios are to be expected in the following areas:

Scenario 1: Production of methenamine and further processing to explosives (4.1.1.2.1)

Scenario 2: Formulation of phenolic resin systems (4.1.1.2.2)

Scenario 3: Production of fuel tablets (4.1.1.2.3)

Scenario 4: Formulation of preparations used as photochemicals or for corrosion prevention (4.1.1.2.4)

Scenario 5: Use of products containing phenolic resin systems (4.1.1.2.5).

The possible exposure during the use of preparations as corrosion inhibitors, as photochemicals (stabilizing agent), as fertilisers, as fungicides, as human medicines or as preservatives in paints, leather and cosmetics is not described in this exposure assessment. Reliable data about the concentration of methenamine in these preparations are not available. In limestone removers and carpet cleaners the concentration of methenamine is below 1%. It is assumed that the concentration of the substance in the other formulations would be also very low. The same holds true for proposed uses of the substance in paints and lacquers (Ullmann, 1995).

4.1.1.2.1 Production of methenamine and further processing to explosives (scenario 1)

The production of methenamine in the large-scale chemical industry takes place continuously in closed systems. The production is based on the reaction of formaldehyde and ammonia in aqueous solution at elevated temperature (up to 95°C). The compound is an aqueous suspension, which is purified by stepwise crystallisation until a purity of 99 %. Then the powdery good is produced by means of spray drying. The substance is placed on the market

in three different qualities: oil-coated (dust-suppressed), crystalline and fine crystalline (Degussa, 1998).

Methenamine is used as a chemical intermediate in syntheses in the large-scale chemical industry, especially for the production of explosives (hexogen, octogen). The further processing mainly takes place in closed systems.

Production operations with the possibility of dust formation are in particular filling and packaging procedures. Bagging is performed automatically from a silo. After being filled and closed the bags were put by hand (small bags, 25 kg) or crane (big bags, 500-1000 kg) into a transport vehicle. Baggers are exposed to methenamine mainly by dust that escapes from the space between the bag and the filling nozzle. Stationary ventilation systems are installed at the bagging station (Merget et al., 1999). All other operations including drying and grinding are performed in closed systems (Degussa, 1998). According to information provided by two producers, filling workplaces are equipped with local exhaust ventilation (LEV) and gloves are used. Furthermore, exposure may occur during sampling, cleaning, maintenance and repair activities.

For the large-scale chemical industry high standards of control at the workplaces are assumed to be practised even if the containment is breached. Exposure may occur during filling, packaging, cleaning, maintenance, repair works and the taking of process samples.

Inhalation Exposure

Workplace measurements

For the operations with a likely exposure at the workplace, measurements are available for different qualities of methenamine (see table 4.1).

Table 4.1 Methenamine exposures at workplaces during production and further processing (provided by two producer, one short-term value was provided)

Job category / activities	Year of measure ment	Number of samples	Range of measurement data [mg/m^3]	Geometric mean [mg/m^3]	95th-percentile [mg/m^3]	Duration and frequency
8-h time weighted average						
Production						
Different operations in production	1995-1997	5	0.01 – 2.0	-	-	-
Inspection room	-	1	0.07			
Filling, packaging						
- fine, normal	1995-1997	29	0.04 – 4.3	-	-	-
- oil-coated	1995-1997	4	0.004 – 0.2	-	-	-
Packaging [1)]	-	2	0.1, 0.2			
Mixing	1995-1997	6	0.14 – 1.52	-	-	-

Job category / activities	Year of measure ment	Number of samples	Range of measurement data [mg/m^3]	Geometric mean [mg/m^3]	95th-percentile [mg/m^3]	Duration and frequency
Storage	1995-1997	2	0.024	-	-	-
Maintenance	1995-1997	1	0.64	-	-	-
Short-term values						
Production	-	-	0.031[2)]	-	-	-

[1)] Quality of methenamine unknown [2)] Duration of measurement unknown

Stationary as well as person related measurements of inhalable dust were performed. For the determination of the methenamine content samples were treated with sulfuric acid, filtrated and the filtrate was diluted with water. In this solution the built ammonia was determined photometrically. The analytical data on methenamine concentrations are to be considered as preliminary as the method used is no standard method and has not been completely validated (Degussa, 1997). The detection limit is unknown.

Based on the available measurement results 4 mg/m^3 is derived as representing the reasonable worst case situation. It is to be assumed, that exposure is lower, if oil-coated (dust-suppressed) powders are used. Based on a rather limited number of available measurements it is assumed that the use of these oil-coated powders result in exposure levels up to 0.2 mg/m³. The indicative character of this exposure estimate has to be stressed; nevertheless, this estimate might be used in order to get an indication for possible exposure reduction with oil-coated powders.

The number of – in general – male workers ranges from 3 to 20 individuals at the different production sites.

Conclusions

During the production of methenamine, exposure to dust at filling is regarded to be the main source of exposure. Based on sufficient measurement data exposure levels are assessed for daily inhalation exposure.

For the purpose of assessing the risks for the use of the powdery substance 4 mg/m^3 (rounded) should be taken and 0.2 mg/m^3, if oil-coated powders are used.

On account of the continuous process, the duration and frequency of exposure are assumed to be daily and for the entire length of the shift.

Dermal exposure

When producing and further processing methenamine dermal exposure could occur during activities like filling, cleaning, maintenance and repair work. For the unprotected worker, according to the EASE model, potential dermal exposure is assessed as follows:

Input parameters: Non dispersive use, direct handling, incidental.
Level of exposure: 0 – 0.1 mg/cm^2/day.

Considering an exposed area of 420 cm^2 (palms of hands) the model yields an exposure level of 0 - 42 mg/person/day.

For assessing actual dermal exposure levels, it has to be considered that the substance is manufactured and further processed primarily in closed systems and that the use of PPE (here gloves and eye protection) is highly accepted in the large-scale chemical industry. The extent of protection by PPE (here gloves) depends inter alia on the suitability of the recommended material with regard to the permeation properties of substance. For the handling of powdery substances, as a rule, the suitability of the gloves can be assumed. As a rough estimation, a protection efficiency of 90 % achieved by suitable gloves is taken resulting in dermal exposure of 0 - 4.2 mg/person/day. The upper value is regarded to represent the reasonable worst case situation.

Conclusions

For assessing the health risks from daily dermal exposure in the area of production and further processing (scenario 1), an exposure level of 4.2 mg/person/day should be taken. This exposure assessment is based on the assumption, that gloves are suitable for the protection against powder.

Exposure to the eyes is largely avoided by using eye protection.

4.1.1.2.2 Formulation of phenolic resin systems (scenario 2)

Phenolic resin systems consist of phenolic resins, methenamine as a hardening agent (up to 15 %) and other powdery substances. These systems are subdivided in phenolic resins, which are placed on the market as thermoset compounds in an uncured form, and phenolic resin moulding compounds, which are purchased in a pre-polycondensated state.

For the production of methenamine modified phenolic resins milled methenamine is mixed with milled phenolic resins at room temperature. The mixture is packed in bags and big bags. The phenolic resin systems can also be placed on the market as liquid preparations.

In case of the production of phenolic resin moulding compounds methenamine is mixed with milled phenolic resins and other powdery substances (e.g. wood flour, pigments). The plastic moulds contain 6 - 8 % methenamine. Operations are carried out batchwise as open, semi-automated processes and include blending of various powder ingredients, fusion polymerisation on a roll at temperatures of 100 – 120°C, and subsequent crushing, grinding and bagging. These preparations are pre-polycondensated, so that the final hardening at the customers site takes only relative short duration. One company states, that 30 male workers were involved. From a second operator it is known that 20 male workers are occupied in the production of moulding compounds (Degussa, 1998).

No information on the use of oil-coated methenamine for the production of phenolic resin systems is available.

During the hardening process (pre-polymerisation), methenamine is decomposed and ammonia as well as possibly formaldehyde are released. The producer states, that the final products do not contain any methenamine. No information is available, if methenamine itself may be released during the hardening process, too.

The formulation to phenolic resins and phenolic resin moulding compounds is not limited to the large-scale chemical companies but is also performed in small and medium-sized companies. For this case, in principle, it cannot be excluded that open systems without local exhaust ventilation are used (Voullaire, Kliemt 1995). It is to be assumed, that gloves and eye protection are not regularly worn and that both, immediate dermal contact and exposure to eyes caused by hand-eye-contacts occur. According to this scenario, inhalative and, as a result of immediate dermal contact, dermal exposures are expected if methenamine and preparations are handled, e.g. during sampling, charging, cleaning, maintenance and repair works. It is known, that metheneamine is filled into bags of different size (25 kg – 1000 kg). No detailed information is available. The following exposure assessment is based on the activity manual dumping of bags or sacks of methenamine (without LEV).

For continuous production frequency and duration of exposure are assumed to be daily and 8 h/shift.

Inhalation exposure

Workplace measurements

Measurement results are not available.

The NL provided results of a study relating to dumping of powdery goods in different formulating facilities (Marquart et al., 1999). These activities are regarded to be comparable to the situation occurring in the production of phenolic resins. In both cases, dumping of powders is considered exposure relevant. The study was aimed neither at very good nor at very bad equipment. The measurements were taken during continuous dumping of powders into mixers equipped with LEV. The measurement values of 1.9 – 27.6 mg/m^3 (shift averages: 0.8 – 12.1 mg/m^3) refer to the handling of 330 – 11369 kg of powders.

EASE estimation

EASE for Windows 2.0, Aug. 1997

EASE estimation for the formulation of phenolic resin products at workplaces without LEV:

Input parameters: T = 20 °C, exposure-type is dust, dry manipulation, LEV absent
Exposure level: 5 - 50 mg/m^3

Conclusions

Since measurement results are not available, manual dumping of powders in a formulating company is taken as an analogy scenario. It should be noted, that often phenolic resins are produced on a large scale basis with mainly automated processes, but for special qualities, also manual dumping seems to be probable. For assessing the risks of daily inhalation exposure, 12 mg/m^3 (highest shift average, round off) should be taken.

If oil-coated powders (dust-suppressed) or liquid preparations are used, it is to be expected that lower exposure occur.

The possible exposure due to evaporation of methenamine during the hardening process is regarded to be negligible compared to exposure to dust.

Dermal exposure

Measurement results on dermal exposure are not available. As an analogy exposure scenario, dumping of powders in a formulation company is taken (Lansink et al., 1996). These activities are regarded to be comparable to the situation occurring in the production of phenolic resins. In both cases, dumping of powders is considered exposure relevant. The field study includes manual dumping of calcium carbonate (several grades) from bags of into paint mixers in ten paint producing facilities (n = 19). Calcium carbonate is a relatively dusty powder. The dumping lasted for 1 – 15 minutes and 2 – 24 bags, containing 10 – 1000 kg calcium carbonate were dumped. Local exhaust ventilation was generally used during dumping. Bags were cut open using a knife and the powder was allowed to flow into the mixer. Exposures due to direct contact with the flow of powder, deposition of the dust and contact with contaminated surfaces, including the outside of the bags. The 90th percentile of the data is used as the basis for the reasonable worst case value. The exposure was determined as 1.9 mg/cm^2 and a total exposure of 3000 mg/person.

Conclusions

For assessing the health risks from daily dermal exposure during the formulation of phenolic resins (scenario 2), an exposure level of 3000 mg/person/day should be taken. The assessment is based on data of an analogous scenario. This exposure assessment is based on the assumption that gloves are not worn.

It cannot be presupposed that eye protection is regularly used. For assessing the risks, hand-eye-contacts as well as possible splashes to the eye should be considered.

4.1.1.2.3 Production of fuel tablets (scenario 3)

A small amount of the produced methenamine is used for the production of fuel tablets which are applied in camping stoves. The tablets contain 97 % methenamine. The production includes the mixture of the powdery substance with additives and the following pressing to tablets.

According to the available information, fuel tablets are only produced in one company in Germany. The production takes place partly in closed systems. Two worker handle the substance 80 days/year for the entire length of the shift.

Measurement data are not available. Therefore, inhalation and dermal exposure are assessed by means of the EASE model.

It is assumed, that worker do not wear gloves regularly. Therefore, dermal exposure is assessed for the unprotected worker.

Generally, worker may potentially be exposed during filling, packaging, cleaning, repair and maintenance work.

Inhalation Exposure

Workplace measurements

Measurement results are not available.

EASE estimation

EASE for Windows 2.0, Aug. 1997

EASE estimation for the production of fuel tablets with LEV:

Input parameters: T = 20 °C, exposure-type is dust, dry manipulation, LEV present
Exposure level: 2 - 5 mg/m^3.

Conclusions

For assessing the risk of inhalation exposure during the production of fuel tablets, 2 –5 mg/m^3 should be taken. The upper value is regarded to represent the reasonable worst case situation. Based on the information from the only producing company in Germany, exposure occurs during 80 days/year.

Dermal Exposure

Dermal exposure is assessed for the unprotected worker using the EASE model:

Input parameters: Non dispersive use, direct handling, intermittent
Exposure levels: 0.1 - 1 mg/cm^2/day.

Considering an exposed area of 420 cm^2 (palms of hands), dermal exposure amounts to 42 - 420 mg/person/day. Based on the information from the only producing company in Germany, exposure occurs during 80 days/year.

Conclusions

For assessing the health risks from daily dermal exposure during the production of fuel tablets (scenario 3), an exposure level of 420 mg/person/day should be taken. This exposure assessment is based on the assumption that gloves are not worn.

It cannot be presupposed that eye protection is regularly used. For assessing the risks, hand-eye-contacts as well as possible splashes to the eye should be considered.

4.1.1.2.4 Formulation of preparations used as photochemicals or for corrosion prevention (scenario 4)

According to the literature (Roempp, 1997) and the Swedish Product Register methenamine is used as a stabiliser in photochemicals and as a component in anticorrosion agents. In contrast, according to an extensive compilation, methenamine is not used in photochemicals in Germany (Baumann, 1990).

Preparations, used as photochemicals and anticorrosion agents are placed on the market as diluted solutions. The concentration of stabilisers and components of anticorrosion agents are low (up to a few percent). Therefore, during production of this preparations only small amounts (< 100 kg) of methenamine are handled.

Exposure is expected during loading, unloading, drumming operations and weighing of the pure methenamine. There is no information if the preparation is produced in a continuous process. The duration of exposure during further processing is assumed to be 1 hour/day.

The formulation to various products may not be limited to the large-scale industries but occur in small and medium-sized companies, too. For this case, in principle, it cannot be excluded that, in addition to the high level of technical protection in the large-scale industry, open systems without local exhaust ventilation are used (Voullaire, Kliemt 1995). It is to be assumed, that gloves and eye protection are not regularly worn and that both, immediate dermal contact and exposure to eyes caused by hand-eye-contacts occur. According to this scenario, higher inhalation and, as a result of immediate dermal contact including hand-eye-contacts, higher dermal exposures are expected if methenamine and preparations are handled, e.g. during filling, sampling, charging, cleaning, maintenance and repair works.

Inhalation Exposure

Workplace measurements

Measurement results are not available.

Exposure scenarios with the handling of rather low quantities of powdery substances in formulating processes are taken for analogy considerations. Such workplaces were subject of an BAuA study on the EASE model (Bredendiek-Kämper, 1999). It turned out, that exposure levels are below 1 mg/m^3 (8 h TWA), if low amounts of powdery substances are handled. This was shown at workplaces in the textile industry, where printing inks are mixed by adding and mixing powdery substances (colour kitchen, typical amounts a few kg).

The NL provided results of a study relating to dumping of powdery goods in different formulating facilities (Marquart et al., 1999). The study was aimed neither at very good nor at very bad equipment. The measurements were taken during continuous dumping of powders

into mixers equipped with LEV. The measurement values of 1.9 – 27.6 mg/m^3 (shift averages: 0.8 – 12.1 mg/m^3) refer to the handling of 330 – 11369 kg of powders.

EASE estimation

EASE for Windows 2.0, Aug. 1997

EASE estimation for the formulation of preparations without LEV:

Input parameters: T = 20 °C, exposure-type is dust, dry manipulation, LEV absent
Exposure level: 5 - 50 mg/m^3

Considering a daily duration of 1 h, exposure levels reduce to 0.7 – 6.5 mg/m^3.

Conclusions

Due to the short duration of the activities carried out, the above mentioned Dutch study (Marquart et al., 1999) seems to be only applicable with limitations. Possibly the lower end of the range of measurement values or shift averages is related to the handling of low amounts of powders (as a rough prediction). Taking the lower end of the ranges (measurement value: 1.9 mg/m^3, shift average: 0.8 mg/m^3) a good agreement with the level assessed with the EASE model is observed.

Exposure to dust inter alia depends on the amount of powdery substance handled during the shift at a workplace. It is to be assumed, that for the production of diluted preparations amounts of < 100 kg/day are necessary. The above mentioned BAuA study (Bredendiek-Kämper, 1999) revealed, that for these scenarios exposure levels are below 1 mg/m^3 (8 h TWA).

Therefore, for the purpose of assessing the risks resulting from inhalation exposure during the formulation of preparations 1 mg/m^3 (scenario 4) should be considered. If oil-coated powders (dust-suppressed) or liquid preparations are used, it is to be expected that lower exposure occur.

Dermal Exposure

Dermal exposure is assessed for the unprotected worker using the EASE model:

Input parameters: Non dispersive use, direct handling, intermittent
Exposure levels: 0.1 - 1 mg/cm^2/day.

Considering an exposed area of 420 cm^2 (palm of hands), dermal exposure amounts to 42 - 420 mg/person/day.

Conclusions

For assessing the health risks from daily dermal exposure during the formulation of preparations e.g. for photochemicals and anticorrosion agents (scenario 4), an exposure level of 420 mg/person/day should be taken. This exposure assessment is based on the assumption that gloves are not worn. The upper value is regarded to represent the reasonable worst case.

It cannot be presupposed that eye protection is regularly used. For assessing the risks, hand-eye-contacts as well as possible splashes to the eye should be considered.

4.1.1.2.5 Use of products containing phenolic resin systems (scenario 5)

Typical applications of phenolic resin systems (containing up to 15 % methenamine) are grinding materials, brake linings, clutch linings, wood glues, laminates and insulation materials. During the process of hardening different moulding processes with the influence of temperature (ca. 110 – 150 °C) and pressure are used, e.g. pressing, transfer moulding, injection moulding and extrusion.

Furthermore, phenolic resin systems are used as binding agents for quartz sand during the production of casting moulds or as binding agents in formed and unformed fireproof materials, e.g. in foundries and the steel industries. The content of methenamine amounts to 0.2 – 0.8 % (Bakelite, 1993).

Powdery phenolic resin systems containing methenamine are added to rubber mixtures as reinforcing resins.

All applications have in common, that powdery preparations with a content of up to 15 % methenamine are filled and/or mixed before the moulding. In some areas, e.g. foundries, liquid preparations are used (Degussa, 1998).

For the above mentioned work places it must be assumed, that LEV is not generally present and protective gloves are not regularly worn. The duration and the frequency of exposure are not known for the particular case.

Inhalation exposure

Workplace measurements

Measurement results are not available.

EASE estimation

EASE for Windows 2.0, Aug. 1997

EASE estimation for the use of phenolic resin systems without LEV
Input parameters: T = 20 °C, exposure-type is dust, dry manipulation, LEV absent
Exposure level: 5 - 50 mg/m^3

Considering a methenamine content of 15 % an inhalation exposure of 0.75 – 7.5 mg/m^3 results.

Conclusions

For the purpose of assessing the risks resulting from daily inhalation 0.75 – 7.5 mg/m^3 (scenario 5) without LEV (exposure levels predicted by the EASE-model) should be considered.

Often exposure relevant activities are carried out for a limited duration and in case not daily. But there is no detailed information and as a result it can not be considered at present. If oil-coated powders or liquid preparations are further processed, lower exposure levels are to be expected.

The possible exposure on account of evaporation of methenamine during the hardening process is assumed to be negligible compared to exposure to dust.

Dermal exposure

Dermal exposure is assessed for the unprotected worker using the EASE model:

Input parameters: Non dispersive use, direct handling, intermittent
Exposure levels: 0.1 - 1 mg/cm^2/day.

Considering a methenamine content of 15 % and an exposed area of 840 cm^2 (hands) the model yields an exposure level of 12.6 – 126 mg/person /day.

Conclusions

For assessing the health risks from daily dermal exposure during the use of phenolic resin systems (scenario 5), an exposure level of 12.6 – 126 mg/person/day should be taken, when considering a content of 15 % methenamine in phenolic resins. This exposure assessment is based on the assumption that gloves are not worn. The upper value is regarded to represent the reasonable worst case.

It cannot be presupposed that eye protection is regularly used. For assessing the risks, hand-eye-contacts as well as possible splashes to the eye should be considered.

4.1.1.2.6 Summary

Based on the available information, 95 % of the produced methenamine is used as a hardening agent in phenolic resin systems. In this, methenamine is decomposed during the hardening processes performed at elevated temperatures.

The main source of exposure is the handling of powdery pure methenamine during the production and formulation (scenarios 1, 2, 4) as well as the use of powdery phenolic resin systems containing up to 15 % methenamine (scenario 5).

2 % of the produced methenamine is further processed to fuel tablets, containing 97 % methenamine. Exposure is possible during the handling of the powdery substance (scenario 3).

The possible exposure during the use of preparations as corrosion inhibitors, as photochemicals (stabilizing agent), as fertilisers, as fungicides, as limestone removers, as carpet cleaners, as human medicines or as preservatives in paints, leather and cosmetics is not described in this exposure assessment. Corresponding exposure scenarios are not defined, because it is not known, whether the uses of methenamine in the mentioned formulations really exist, and, if they do, the concentration of methenamine is considered to be very low.

The relevant inhalation and dermal exposure levels are given in the tables 4.2 and 4.3, respectively.

Measurement results concerning inhalation exposure were only available for the production of the substance (scenario 1). The data basis is sufficient to be regarded as representative. For scenario 2 “Formulation of phenolic resin systems”, analogous data were taken into account. For both scenarios, the task charging of reaction vessels with powders substances is regarded to be the main source of exposure.

Dermal exposure for the production of the substance was assessed in consideration of a high level of protection realised in the large-scale chemical industry and with the assumption that suitable gloves are regularly worn. A protection efficiency of 90 % is assumed.

In all other sectors, exposure levels are assessed for the unprotected worker based on the assumption that gloves are irregularly worn.

Table 4.2: Summary of inhalation exposure data (reasonable worst case) of methenamine which are relevant for occupational risk assessment

Inhalation exposure								
Scenario, Area of production and use	**Form of exposure**	**Activity**	**Duration**	**Frequency**	**Shift average [mg/m³]**	**Method**	**Short term [mg/m³]**	**Method**
Production an use as a chemical intermediate								
1. Production and further processing to explosives (with LEV)	dust	charging, filling, cleaning, repair,	shift	daily	1 a) 4	highest measurement result (round off), dusty material	-	-
			shift	daily	1 b) 0.2	highest result low dust material; indicative value		
Formulation								
2. Formulation of phenolic resin systems	dust	charging, drumming, packaging, cleaning, repair, maintenance	shift (assumed)	daily (assumed)	12	analogous data	-	-
3. Production of fuel tablets (97 % methenamine)	dust	filling, packaging, cleaning, repair, maintenance	shift	80 days/year	5	EASE with LEV	-	-
4. Production of formulations used in corrosion prevention and as photochemical	dust	filling, weighing	1 h/shift (assumed)	daily (assumed)	1	analogous data	-	-
Use of formulations								
5. Use of phenolic resin systems (up to 15 % methenamine)	dust	charging, repair cleaning, maintenance	shift (assumed)	daily	7.5	EASE without LEV	-	-

Table 4.3: Summary of dermal exposure data (reasonable worst case) of methenamine which are relevant for occupational risk assessment

Dermal exposure								
Area of production and use	**Form of exposure**	**Activity**	**Frequency [days/year]**	**Contact level [1]**	**Level of exposure [mg/cm^2/day]**	**Exposed area [cm^2]**	**Shift average [mg/p/day]**	**Method**
Production and further processing								
1. Production and further processing to explosives	dust	charging, repair, drumming, cleaning, sampling	daily	incidental	0 – 0.1	420	4.2	EASE (90 % protection by suitable gloves)
Further processing to formulations								
2. Formulation of phenolic resin systems	dust	charging, drumming, cleaning, repair, packaging, maintenance	daily	intermittent	1.9	1600	3000	Analogous data
3. Production of fuel tablets (97 % methenamine)	dust	filling, packaging, cleaning, repair, maintenance	80 days/year	intermittent	0.1 – 1	420 (palms of hands)	420	EASE (without gloves)
4. Production of formulations used in corrosion prevention and as photochemical	dust	filling, weighing	daily	intermittent	0.1 - 1	420 (palms of hands)	420	EASE (without gloves)
Use of formulations								
5. Use of phenolic resin systems (up to 15 % methenamine)	dust	charging, cleaning repair, maintenance	daily	intermittent	0.1 - 1	840 (hands)	126	EASE (without gloves)

[1] contact level according to the EASE model

4.1.1.3 Consumer exposure

The Swedish product register gives 3 products for use in the consumer area out of a total of 84 products (1996). In the BfR data base 4 products for use in the consumer area out of a total of 24 products were found (BfR, 2004), cosmetics excluded.

Methenamine is used as an auxiliary ingredient in one remover of limestone from coffeemachines (< 1%) and in two Steam Vac floor and carpet cleaners (< 1%). In one case methenamine is used in the pure form in solid fuel.

No exact number of cosmetic products can be provided for methenamine, because the substance is included as preservative in framework formulations. The substance is present in an estimated number of 50 cosmetic products.

Inhalation exposure

Taking into consideration the vapour pressure, the Henry coefficient and further physicochemical properties of the substance inhalative exposure by use of consumer products can be neglected.

Dermal exposure

Dermal exposure may be derived from use as solid fuel, as limestone remover, and as ingredient in cleaners and in cosmetic products.

For solid fuel tablets containing methenamine repeatedly local dermal exposure may occur to some users in connection with handling/ breaking the tablets for a short time (within seconds).

In connection with the use of limestone removers for coffee machines occasional short-time dermal exposure may occur in connection of handling the limestone remover during use. The exposure is considered to be to a very small area of the hands and thus the dose available to systemic absorption may be considered negligible. The short-time local skin contact to very low levels of methenamine during this use is considered to be negligible for risk characterisation purposes.

Direct exposure from Steam Vac floor and carpet/upholstery cleaners can be excluded during use with adequate application. However, dermal exposure may occur from direct contact with e.g. furniture covering, which have been cleaned with Steam Vac floor and carpet/upholstery cleaners. After use residual amounts may be present in the textile.

Exposure to carpet/upholstery cleaners

The possible residual amount of methenamine on the upholstery can be estimated as follows:

For a surface of 1 m² approximately 200 g cleaning solution is needed (~185 ml water and ~ 15 ml cleaner concentrate). This leads to a load of 15 µg/ cm², considering the weight fraction of methenamine < 1% in cleaner concentrate. It is assumed that 20 % remains on the surface and partly migrated to the upholstery, that means 3 µg methenamine remains per cm².

For the estimation of dermal exposure the following scenario is used:

The contact area of a person sitting in an armchair with cleaning upholstery accounts for about 1.000 cm² (half of both forearms and hands).

A four hour contact (e.g. during watching TV) would lead to an amount of 30 µg/event (3 µg x 1000 cm² x 0.01), presupposed a migration-rate of 1% per event.
Taking 100 events into account, the yearly total amount of methenamine migrating from the upholstered armchair to the skin accounts for 3000 µg, resulting in an average external dermal exposure of ~ 0.14 µg/kg bw per day assuming a body weight of 60 kg. This amount can be neglected for risk characterisation purposes in relation to the amount by exposure to cosmetics.

Exposure to cosmetics

Dermal exposure due to cosmetics may derive by use of lotions, creams and make up. According to the Council Directive 76/768/EEC, Annex VI, the maximal allowed concentration of methenamine as preservative in a cosmetic product is 0.15%.

The estimation of exposure by cosmetics based on the SCCNFP approach. In the specific case of preservatives the SCCNFP calculated a global daily exposure value for all cosmetic products that one person may daily apply on the skin. In a worst-case scenario, considering the consumer would use a set of cosmetic products containing the same preservative, the SCCNFP-value accounts 17.79 g/day (SCCNFP/0321/00, Final). With consideration of the weight fraction of methenamine 0.15% and the body weight of 60 kg the external exposure can be calculated to 445 µg/kg bw/d.

Oral exposure

Exposure by eating food

According to § 28 of the German cheese-directive (1986) methenamine is allowed as preservative (E239) in provolone cheese in a quantity of 25 mg/kg (calculated as formaldehyde). It is not allowed in other food. The daily intake of provolone cheese accounts about 50 g (99th percentile of the estimated daily consumption quantity, determined by the German National Food Consumption Study (1985-1988) (Adolf et al. , 1995).

This daily intake would lead to a possible intake of 1.25 mg of methenamine per day and corresponds to the external exposure. The assumption that 100% of methenamine are absorbed, leads to an internal exposure of ~ 21 µg/kg of bw per day.

Exposure via medical treatment

Methenamine is used in human medicine to treat urinary tract infections with oral doses of 2 - 4 g/day, corresponding to up to 57 mg/kg bw/day (cf. 4.1.2.6).

Conclusion

The main route of exposure for consumers is the dermal one using cosmetics containing methenamine as preservatives. The external exposure of skin can reach a value up to ~27 mg

corresponding to 0.445 mg/kg bw and day (body weight 60 kg). Dermal exposure to methenamine for very short times may also occur during the application (handling/breaking) of solid fuel tablets containing methenamine. Possible dermal exposure to residual amounts of the substance on textile materials after use of carpet/upholstery cleaners was estimated to be very low and will be neglected for risk characterisation purposes.

Oral exposure due to eating provolone cheese can lead up to a daily intake of 1.25 mg resulting in an internal exposure of up to 0.021 mg/kg bw and day.

4.1.1.4 Indirect exposure via the environment

Releases of methenamine into the environment following production, formulation and processing were calculated in chapter 3. The indirect exposure of humans via environment, i.e. through food, drinking water and air is considered to be very low. Methenamine does not adsorb, is not bioaccumulative and is not expected to persist in the environmental compartments.

The target compartment is water, a release into air can widely excluded. If released into air, e.g. by accident, a quick degradation to formaldehyde and ammonium is expected. Hence, the risks arising from these substances as degradation products needs to be addressed, too.

However, it needs to be emphasised that formaldehyde itself is produced in 5-6 millions t/a. The production of methenamine is 30.000 t/a. If it was assumed that all methenamine was completely transformed into formaldehyde the contribution was < 1% to the production of formaldehyde. Hence, it is preferred to assess the risks of formaldehyde not in this report.

4.1.1.5 (Combined exposure)

For the consideration of combined exposure, occupational exposure in combination with dermal exposure via cosmetic products might be relevant. Using the assumptions detailedin 4.1.1.3, this could result in an additional body burden for workers of up to 13 mg/person/day. Additional oral exposure from provolone cheese seems negligible, as does indirect exposure via the environment.

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

4.1.2.1 Toxico-kinetics, metabolism and distribution

Absorption

Methenamine and its salts (e.g. methenamine mandelate or methenamine hippurate) are rapidly absorbed from the intestinal tract.

After oral administration of a single dose of 1 g methenamine hippurate (about 450 mg base) to four volunteers (Allgen et al., 1979), maximal plasma levels of 70 – 100 µmol/l were reached within 1 to 2 h, the concentrations declined with a half-life of about 4 h. The average distribution volume was about 0.6 l/kg which is close to the total body water in adults. After multiple dosing of methenamine hippurate (1 g methenamine hippurate every 12 h over a total period of 3 d), about 80% of the dose administered each period was recovered in the urine within 12 h thereafter indicating that at least this amount has been absorbed. The methenamine determination in serum and urine was based on hydrolysis of the compound to formaldehyde in acid solution and subsequent colorimetric determination of formaldehyde. It should be noted that this method for determination will include any "free" formaldehyde present in the sample (see also Gollamudi et al., 1981).

In a well documented pharmacokinetic study (Klinge et al., 1982), ten healthy volunteers, 6 women and 4 men, were given two formulations of methenamine hippurate as a single dose (1 g, about 450 mg base) on the first day and thereafter 1 g twice daily for 8 d, and - after a treatment-free period of one week - the second formulation was administered for another 8 d. After a single dose maximum serum concentration was achieved in about 1 h. The mean half-life in blood was reported as 4.3 h. The distribution volume was 0.56 l/kg. On successive daily application approximately 90% of the dose was excreted in the urine during each 12 h dosing interval. Methenamine itself was determined by gas chromatography from serum and urine samples.

Gollamudi et al. (1981) determined the urinary excretion of both methenamine and formaldehyde for 48 hr after the oral administration of 10 different methenamine products (active ingredients were methenamine or its mandelate or hippurate) to ten human volunteers in a crossover study. There were no significant differences ($p > 0.05$) among methenamine and its various salts in terms of the cumulative excretion of total methenamine (about 70 to 83% of the dosis) or the total excretion of "free" formaldehyde (about 5.5% of the dosis).

Distribution

Methenamine can slowly pass the placenta, is detectable in the amniotic fluid and in breast milk. The methenamine concentrations in breast milk of lactating women was found to be in the same range as found in maternal plasma. Therefore the authors concluded that no accumulation of methenamine occurs in milk (Allgen et al., 1979).

Metabolism

From the distribution-excretion-balance, it can be assumed that approximately 10-20 % of an oral dose of methenamine is converted to formaldehyde and ammonia in the stomach (Gleckman et al., 1979). Gandelman administered methenamine mandelate to healthy men as oral doses of 1 g, 4 x daily. The pH of the inhibitory urine specimens ranged from 5.7 to 6.2. The average content of „free“ formaldehyde was about 6% in urine.

No data are available from detailed studies, but ingested formaldehyde, which is formed in amounts of about 10 – 20 % from an oral dose of methenamine, is rapidly taken up and metabolized as shown by the blood increase of formate in dogs (Restani et al., 1991). The

time of transformation of formaldehyde into formic acid, its principal metabolite, is only 1 min in many animal species including man. The half-life of formic acid is 55 min (Restani et al., 1991).

It has been postulated that bis(chlormethyl)ether may be formed in the stomach from the reaction of formaldehyde with chloride ions (Hanselaar et al., 1983). This seems to occur easily when the chemical is in the gaseous phase but less so in liquid phases (Travenius,1982). The ether was not detectable in liquid phases (detection limit 10 ppb in aqueous solution and 1 ppb in gaseous medium respectively, Tuo et al., 1974).

Some studies examined the effect of the pH in the urine on the conversion rate of methenamine to formaldehyde in vitro and in vivo when used as medicinal antimicrobial agent (Gandelman, 1967; Gollamudi et al.,1981; Musher et al., 1974; Strom et al., 1993). In an acidic medium, the rate of hydrolysis of methenamine to formaldehyde and ammonia is dependent on pH. The hydrolysis occurs more rapidly at lower pH values(e.g. after oral administration to man in the stomach and the urine).

Musher et al. (1974) as well as Strom et al. (1993) studied the methenamine metabolism in vitro. Both groups have shown that in an acidic medium methenamine is hydrolyzed at a rate which is primarily dependent on pH. The dynamics of the urinary tract is also important. But the dosage form (base or salt) plays a minor role. Bactericidal concentrations of formaldehyde in urine (>28µg/ml) were achieved in 3 h in urine of pH 6.0 containing methenamine at 750 µg/ml. The half-life of methenamine conversion to formaldehyde increased approximately 20 times from 20 h at pH 5.0 to about 400 h at pH 6.5 (Strom et al., 1993).

Excretion

After multiple dosing of methenamine hippurate (1 g) for 3 d, about 80% of the dose administered each period was recovered in the urine within 12 h thereafter indicating that at least this amount has been absorbed. The methenamine determination in serum and urine was based on hydrolysis of the compound to formaldehyde in acidic solution and subsequent colorimetric determination of formaldehyde. It should be noted that this method for determination will include any "free" formaldehyde present in the sample (see also Gollamudi et al., 1981).

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Gollamudi et al. (1981) determined the urinary excretion of both methenamine and formaldehyde for 48 hr after the oral administration of 10 different methenamine products (active ingredients were methenamine or its mandelate or hippurate) to ten human volunteers in a crossover study. There were no significant differences ($p > 0.05$) among methenamine and its various salts in terms the cumulative excretion of total methenamine (about 70 to 83 % of the dosis)or the total excretion of "free" formaldehyde (about 5.5 % of the doses).

Conclusions

Methenamine is rapidly absorbed (90% of the dose within 12 h) and excreted mostly unchanged in the urine after oral uptake in man. Approximately 10 – 20 % of an oral does of methenamine is converted to formaldehyde.The mean half-life in blood was reported as 4.3 h. Methenamine can pass the placenta and is detectable in breast milk of lactating women, however, no accumulation was seen. There are no data from studies following dermal administration or inhalation exposure of methenamine. As a default for dermal absorption a value of 50% absorption will be assumed based on the chemical structure and the physico-chemical data: molecular weight (140 g/mol), water solubility (667 g/l), partition coefficient (log Pow - 4.15), and a cationic ionisation state (an aqueous 1 N solution has a pH of 9.5 according to Degussa, 1998). The systemic availability after oral administration is assumed to be 100%, whereas that after inhalation is set at 100% (default).

4.1.2.2 Acute toxicity

Animal data:

Oral

Two groups of five rats were given 10 g/kg and 20 g/kg of methenamine as an 80% aqueous solution by oral intubation. All animals survived (Della Porta, 1966). In conclusion, the oral LD50 is greater than 20000 mg in rats. No other details are available. The study was conducted in 1966 before OECD Guidelines existed.

Inhalation

No data available.

Dermal

In a limit test, 5 female and 5 male rats survived occlusive skin contact with 2000 mg/kg bw of an aqueous preparation for 24 hours. Clinical signs were not noted. At necropsy, no alterations were detected, but a yellowish discoloration at the application site was still present at day 14 after exposure to the substance (Degussa AG, 1997). The study was conducted according to OECD Guideline 402. In conclusion, the dermal LD50 after semi-occlusive 24-hour application is greater than 2000 mg in rats.

Human data:

Methenamine caused acute dermatitis in 60 male employees in a local rubber factory. On the head (forehead, cheeks and sides of the neck) as well as the exposed parts of the arm (entire forearm, back of the hand, area between the fingers) the initial symptom was redness, followed by fine, watery vesicles, and later edema. Extreme itching was the principle symptom reported. Later, many of the persons affected had indolent, deep infections that proved resistant towards treatment. Removal of methenamine from the entire rubber stock prevented further cases. Systemic toxicity was not observed (Cronin, 1924).

Conclusion:

Limited data on the acute toxicity of methenamine in humans are available. Acute dermatitis of the exposed surfaces was the main symptom.

Acute toxicity in rats was demonstrated to be very low after oral and dermal application with LD50 values of > 20 g/kg bw and 2 g/kg bw, respectively. Data on inhalation toxicity of methenamine are not available.

4.1.2.3 Irritation

Animal data:

No skin irritation either on the intact or on the abraded skin of 3/3 rabbits was noted after a 4 hour occlusive exposure with 0.5 g substance moistened with water according to OECD Guideline No. 404. No systemic effects were noted (Degussa, 1984a). Long lasting (24 hours) occlusive skin contact resulted in slight irritation in 6 male rabbits even with a 0.2 % aqueous solution of the substance. This effect may be due to the formation of formaldehyde and ammonia under these circumstances (Zondlo, 1992).

In a Draize eye irritation test with 3 rabbits and 0.1 g substance each no irritation and no systemic effects were detected. Hypersecretion occurred in all 3 animals shortly after application, which was reversible within 24 hours (Degussa AG, 1984b).

In rabbits, methenamine does not exhibit local irritation to skin or eyes under the conditions of animal tests performed according to international guidelines.

Human data:

In a case study reported by Merget et al. (1999), irritant dermatitis of the hands, predominantly of the palmar parts was observed in all highly exposed workers. However, it should be recognized that the number of persons included in the study is limited. Since high- and low-dose exposure groups were defined on the basis of the type of occupational function, assessment of quantitative dermal exposure of persons affected is difficult. Accordingly, also positive cases were reported in the low exposure group.

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Rubber workers exposed to methenamine-resorcinol-mixtures reported an excess of acute symptoms. Symptoms associated with handling the mixtures included itching and skin rash. However, no direct causal relationship could be drawn between the observed adverse effects and any specific responsible agent (Gamble, 1976, for more details, refer to 4.1.2.6).

The data on irritation caused by fumes containing methenamine and its decomposition products ammonia and formaldehyde may reflect mainly the well known irritative properties of these decomposition products (Dreyfors et al., 1989). Hydrolysis of methenamine may also occur upon contact to skin.

Conclusion:

Methenamine is not a local irritant by contact with skin and eyes of rabbits. In contrast to available animal data, occupational dermal exposure of methenamine in humans provides some evidence that methenamine causes local skin irritancy. After contact to human skin and

sweat, methenamine may be hydrolyzed forming formaldehyde and ammonia. It is therefore possible that the reported adverse effects are caused by the metabolites formaldehyde and ammonia. Due to the low quality of available human data classification as “irritating” (Xi) and labelling with R38 is not warranted.

4.1.2.4 Corrosivity

Animal data:

Studies on skin irritation demonstrated that methenamine is not a corrosive substance. In rabbits, methenamine does not exhibit local irritancy to skin or eyes (Degussa AG, 1984a, 1984b).

Human data:

Case studies showing dermal exposure and skin irritation in humans demonstrated, that methenamine is not a corrosive substance (Merget et al., 1999, Cronin, 1924, Gamble, 1976).

Conclusion:

Methenamine has no corrosive properties.

4.1.2.5 Sensitisation

Animal data:

A guinea pig maximization test (GPMT) according to OECD Guideline 406 was performed with 20 guinea pigs in the test group and 10 guinea pigs in the control group, using methenamine of > 99% purity. Intradermal induction was performed on day 1 with 0.1 ml of a 30% methenamine solution in physiological saline. For epidermal induction on day 8, 0.5 g of the substance was mixed with 0.4 ml physiological saline forming a paste, which was covered by an occlusive patch. Epidermal treatment caused mild-moderate erythema in 15/20 animals. Challenge application was performed on day 22, using a non-irritating 50% solution of methenamine in physiological saline. 24 hours after challenge, 15/20 animals showed mild-moderate erythema; 12 animals simultaneously showede mild-moderate edema. 48 hours after challenge 2 additional animals showed erythema and one additional animal showed an edema. At this time point, erythema and edema were reversible in 3 and 6 animals, respectively, resulting in an overall challenge sensitization rate of 15/20 animals (75%). No skin reactions were observed within the control group; none of the test or control animals exhibited systemic toxic effects. This study demonstrates that methenamine is a strong skin sensitizer in guinea pigs (Degussa AG, 1985).

In a Local Lymph Node Assay (LLNA) according to OECD Guideline 429, an EC3 (test concentration, which causes a Stimulation Index (SI) of the auricular lymph nodes of 3.0) of

30.6% was determined for methenamine, while an EC3 as low as 0.96% was determined for formaldehyde in the same study. The test was performed treating young adult (6-8 weeks of age) female BALB/c mice with methenamine dissolved in a acetone-olive oil mixture (4:1). Test concentrations were 2.5, 5, 10 and 20%. In order to enhance possible low responses of weak sensitizers animals were pretreated with sodium dodecyl sulfate 1% (SDS) on the dorsum of the ears one hour before administration. Results of the LLNA affirm the classification of methenamine as a skin sensitizer (de Jong et al., 2005).

Animal data on sensitization by inhalation are not available.

Human data:

In 1992/1993 among 2150 patients with dermatitis tested for methenamine sensitivity (1% in petrolatum) 27 (1.3%) showed a positive skin reaction. Out of these, 15 (0.7%) were interpreted as irritant reaction and 12 patients (0.5%) were regarded as sensitized. In 1994/1995, among 3082 persons tested, 38 (1.2%) showed positive skin reactions with methenamine Out of these, 15 (0.5%) were interpreted as irritant reactions and 23 patients (0.8%) were regarded as sensitized (IVDK, 1996).

Within a study related to rubber-related allergic contact dermatitis, patch-testing was performed with a number of rubber-related substances. Out of 309 patients, 1.9% showed positive skin reactions with 2% methenamine (Holness and Nethercott, 1997).

A 54-year-old employee with an itchy eruption on his hands, neck and shoulders was presented in March 1987. He had worked in a foundry for 10 years being engaged in a core molding process and had developed itchy eruptions on the dorsum of his hands, neck and shoulders 3 years ago. The eruptions and itching were aggravated by sweating. His work was making a mixture of sand, phenolic resin, methenamine and lubricant, and he was often covered with the mixture. Offensive stench gas was evaporated from the heated sand core. Open patch testing and closed patch testing with raw materials and chemicals detected within the gas from the heated sand core were performed. The patient reacted positive to 1% methenamine in petrolatum, but did not react positively to formaldehyde. Repeated patch testing in October 1987 confirmed the negative reaction to formaldehyde (Hayakawa et al., 1988).

In one molding resin producing factory, 10% of the workers were affected with dermatitis during a period of one year. Patch tests with various types of resins performed on 10 cases showed that sensitivity to methenamine and to formaldehyde was the cause of 80% of the dermatitis in this plant (Schwartz, 1957).

Methenamine adversely affected 60 employees in a local rubber factory. Acute dermatitis of the exposed surfaces was the principle symptom: Removal of methenamine from the entire rubber stock alone prevented further cases (Cronin, 1924). However, it cannot be concluded from this case study that dermal irritation was caused by sensitization.

The total number of cases observed in a report on the shellac and lacquer industries amounted to 7 patients each, all of whom manifested allergic symptomatology upon separate exposure to ethylenediamine and methenamine. A skin test with 1% dilutions gave severe positive reactions, characterized by immediate wheal formation. The provocative inhalation test with methenamine was positive in 7/7 patients. On exposure to the substance, the patients showed either wheezing and heaviness on the chest or severe asthma, allergic coryza, or skin

manifestations of allergy. 14 patients from the beauty industry were also challenged with methenamine and other substances. Of these, 13 showed diverse positive responses. However, since there was exposure to several chemicals, cross-reactivity may have occurred.

In a factory where machines for the processing of chemicals are produced, a worker who tested a machine with chemicals used for the preparation of rubber was exposed directly after the chemicals had run through the machine. He suffered from coughing and wheezing resulting in three consecutive severe asthma attacks after repeated exposure (Gelfand, 1963). Due to the study limitations (only a few case reports, no detailed description of the exposure level of the individuals affected, and possible contributions of other substances in addition to methenamine to positive findings) no clear conclusion on respiratory sensitization can be drawn from this study (cf. also 4.1.2.6).

A more recent study was designed to assess the health effects of methenamine on the airways and the skin of workers in the chemical industry (Merget et al., 1999). 17 “highly” exposed and 16 “low” exposed employees of a methenamine producing plant were examined (a quantification of high or low exposure is not given). Among the 17 highly exposed persons 8 subjects were baggers, 5 were shift leaders and 4 were executive staff. 11 blue collar and 5 white collar workers with no exposure to known sensitizers were recruited as controls.(n = 16). Four persons, who had left the production department and another 15 who had left the plant for reasons not related to methenamine exposure, were also included (n = 19). Medical history, total and specific IgE to four environmental allergens, lung function and bronchial responsiveness to metacholine were assessed by standard procedures. Lung function was evaluated by measurement of forced expiratory volume in 1s and maximal expiratory flow at 50% of forced vital capacity (pneumotachograph, CustoVit, CustoMed, Munich, Germany). Measuring conditions and reference values were chosen as described recently (Quanjer et al., 1993). Bronchial hyperresponsiveness was assessed as described in Merget et al. (1996) with two modifications: methacholine was used instead of histamine and maximally 31 instead of 63 cumulative breaths of the 8 mg/mL methacholine solution were administered. Skin prick tests were performed with known sensitizers and methenamine. 64.7 % of the exposed subjects and 68.8 % of the controls reported symptoms during the year before the study began, most of them not related to work. Work-related symptoms and objective parameters did not show differences between groups, and skin tests showed no sensitization to methenamine (for results on skin irritation, see section 4.1.2.3). Among those who had left methenamine production for medical reasons, two former baggers showed sensitization to methenamine by patch test and reported eczema during exposure which disappeared after removal from exposure. Geometric mean methenamine concentrations were 0.3 mg/m^3 in shiftleaders and 0.6 mg/m^3 in baggers. It was concluded that high exposures to methenamine may cause allergic contact dermatitis. However, there was no evidence of an increased risk for occupational asthma at airborne concentrations in the range of 0.2 - 2.6 mg/m^3 (Merget et al., 1999).

Conclusion:

Methenamine has demonstrated some skin sensitizing potential in humans. Guinea pigs exhibited strong skin sensitization in a maximization test with a 50% aqueous substance solution. In a Local Lymph Node Assay (LLNA) a positive effect concentration (EC3) of 30.6% methenamine was derived. A comparably low EC3 for formaldehyde was determined

in the same study. Thus, it may be concluded that also for skin sensitization formaldehyde, which may be generated by hydrolysis of methenamine in contact to skin, and not methenamine, is the main causative agent of sensitization. The existing classification with R 43 "May cause sensitization by skin contact" is warranted.

From earlier studies a number of cases of allergic symptoms such as wheezing and asthma were reported upon exposure to methenamine (Gelfand, 1963). However, in all cases exposure to other irritant and sensitizing chemicals occurred simultaneously. The respiratory hypersensitivity could not specifically be related to methenamine exposure. From a well-documented recent study that was designed to analyse the sensitizing potential of methenamine, there was no evidence that methenamine alone may cause respiratory sensitization after occupational exposure (Merget et al., 1999). This study was considered to be of higher validity than the earlier Gelfand reports. In consequence, there is not clear evidence of a respiratory sensitization potential of methenamine at airborne levels present at contaminated workplaces.. Classification with R 42 „May cause sensitization by inhalation“ does not seem warranted.

4.1.2.6 Repeated dose toxicity

4.1.2.7 Repeated dose toxicity

Animal data:

The available repeated dose toxicity studies on methenamine used the oral route (gavage, feeding, drinking water) of exposure. There are no data of repeated dose toxicity studies in experimental animals which meet the requirements of standard repeated dose toxicity testing protocols or were performed according to currently accepted test designs. In addition, there are several long-term/lifetime studies designed for examination of carcinogenicity. For long-term studies, see also 4.1.2.8.

Oral

Gavage studies (rat)

90-day and 333-day study

In a comparative investigation multiple routes of administration were studied. Two groups of BD (cPah) rats were treated by gavage with 400 mg methenamine (purity unspecified) per animal. The first group, 5 males and 5 females, received a total dose of 28.8 g methenamine for 90 days and the second group, 15 males and 15 females, 94 g methenamine for 333 days, Assuming a mean body weight of 250 g for male rats and 180 g for female rats, the mean dose for 90 days was estimated to be approximately 1280 mg/kg bw/d for males and 1780 mg/kg bw/d methenamine for females, and for 333 days the mean dose of methenamine was 1130 mg/kg bw/d for males and 1570 mg/kg bw/d for females. Data of hematology and clinical biochemistry tests were not available. There were no methenamine-induced mortality and no differences from controls in behavior, body weight gain and feed consumption in rats of both sexes treated with methenamine in the subchronic as well as in the chronic oral study up to 1780 mg/kg bw/d. The only clinical sign observed in animals given methenamine was a citrus-yellow discoloration of the hair coat. No differences in macroscopic lesions in the main organs of animals of the test and control groups were observed. No data on methenamine-induced histopathological findings were available. Based on the results of these studies, the no-observed-adverse-effect-level ($NOAEL_{sys}$) for methenamine is considered to be at approximately 1130 mg/kg bw/d in males and 1570 mg/kg bw/d in female BD (cPah) rats (Brendel, 1964).

Diet studies (rat and cat)

Lifetime study

Rat

Groups of 16 male and 16 female Wistar rats were given either 0 or 0.16% (equivalent to 0, or about 100 mg/kg bw/d in both sexes, based on a body weight of 420 g in male and 280 g of female rats and a mean consumption of 42 mg methenamine/day in males and 29 mg in females) methenamine (commercial grade purity) in a standard diet from weaning (two months old) to natural death. Body weights were taken at approximately 3-months intervals

and at death. Organ weights of livers, kidneys, adrenals and gonads were determined at autopsy. Histological studies were carried out on tissues showing abnormalities. Data on hematology and clinical chemistry were not available. General health and behavior as tested by activity in revolving drum at the age of 1, 3, 7, and 14 months showed no significant differences between controls and methenamine treated animals. A yellow staining of the perineal hair was observed in one male and three female rats treated with methenamine. No significant differences were observed between methenamine treated animals and control with respect to body weight, organ weights, histopathological findings, life-span and causes of death.

In an additional palatability experiment, rats were allowed to choose between food containing methenamine and the same food without methenamine for a 28-day period. The two types of food were consumed in comparable amounts. After a 120-day period during which they were fed only the methenamine enriched diet, the animals were again allowed to choose between the two diets in a second 28-day trial. The addition of methenamine had no effect on palatability of the diet.

Thus, in the chronic oral toxicity study in Wistar rats a $NOAEL_{sys}$ of 100 mg/kg bw/day for methenamine was found for both sexes (Natvig et al., 1971).

Long-term study

Cat

In a comparative study one group of two male and three female cats (strain unspecified) received feed containing 1250 mg methenamine (commercial grade purity) per kg feed. Each cat received a total dose of 180 g methenamine for 742 days. Assuming a mean body weight of 4 kg for both sexes, the mean dose per cat for a period of two years was estimated to be approximately 60.65 mg/kg bw/d methenamine. Another group of cats, one male and three females, were fed a diet containing 374 mg formaldehyde per kg feed for 106 weeks (equivalent to approximately 20.88 mg/kg bw/d for both sexes, based on feed consumption resulting in a total dose of 62 g per cat). A third group of three male and female cats served as control. One female in the formaldehyde group died after seven months of pleurisy and a female in the methenamine group died after twenty-three months of a pyrogen infection in the nasal cavity and paranasal sinuses. No treatment-related effects were found concerning food consumption, body weight gain, or behavior in animals treated with methenamine. There were no data on hematology, biochemistry and histopathology. Thus, it was concluded that 60.65 mg/kg bw/d methenamine is the overall $NOAEL_{sys}$ for male and female cats (Kewitz, 1966, unpuplished report).

Drinking water studies (rat and mouse)

To detect possible chronic toxic effects and to identify target organs of methenamine toxicity, the substance (commercial grade purity) was administered in the drinking water, provided ad libitum, over periods of up to 104 weeks to rats and 60 weeks to mice of various strains. After termination of the treatment experimental animals of both species and sexes were observed for different periods of time (e.g. for the remainder of their lifetime) to recognize reversibility, or delayed occurrence of toxic effects.

Rat

2-week treatmen- period

12 male and 12 female outbred Wistar rats (10 weeks old) received a high concentration of 5.0% methenamine (equivalent to 5000 mg/kg bw/d, based on body weights of 250 g in males and 200 g in females and an average water consumption of 10% of the body weight) daily in the drinking water for two weeks with a subsequent 102-week treatment-free period. Necropsy was performed on all animals that died during the study or were killed at termination. Organ samples and all gross lesions taken at necropsy were evaluated microscopically. About 50% of the rats of both sexes died within one week after treatment. Specific causes of death were not reported. Surviving rats recovered rapidly and showed no toxic effects. The only clinical observation was a citrus-yellow discoloration of the hair coat which is of no toxicological relevance. Data on hematology and clinical biochemistry were not available. Growth, necropsy and histopathology of the treated animals showed no specific changes due to administration of methenamine. Thus the LOAEL for two weeks was 5000 mg/kg bw/d methenamine in male and in female outbred Wistar rats (Della Porta et al., 1968).

50-week treatment period

Groups of 15 male and 15 female Sprague-Dawley rats (8-10 weeks old) received on 5 days/week 0.1% methenamine in drinking water or 0.1% methenamine with 0.2% sodium nitrite in drinking water (no data of negative controls). Animals were treated for 50 weeks (a total of 250 days) and kept until they died or were killed due to moribund condition. Each rat received a total of 5 g methenamine over 50 weeks (equivalent to 80 mg/kg bw/d in males and 100 mg/kg bw/d in females, calculated on an assumed body weight of 250 g in males and 200 g in females). There were no data on hematology and clinical biochemistry. A complete necropsy and histopathologic examination was performed from all experimental animals. There was no significant difference in the survival rate. The chronic oral administration of methenamine to Sprague-Dawley rats at dose of 80 mg/kg bw/d for males and 100 mg/kg bw/d for females resulted in no effects on body weight gain, behavior, macroscopic or microscopic findings. Therefore, it was concluded that 0.1% methenamine (equivalent to 80 mg/kg bw/d in males and 100 mg/kg bw/d in females) was established as the no-toxic-effect-level ($NOAEL_{sys}$) for Sprague-Dawley rats (Lijinsky and Taylor, 1977).

104-week treatment period

Groups of 48 male and 48 female outbred Wistar rats (10 weeks old) received 0, or 1.0% methenamine in the drinking water for 104 weeks (calculated intake 2.0-1.5 g/kg bw/d in males and 2.5-2.0 g/kg bw/d in females). After the termination of treatment rats were observed for a subsequent treatment-free period of up to 3 years of age. Animals were inspected daily and weighted every two weeks. Water intake was determinated periodically (no further information). There were no data on hematology and clinical biochemistry. Necropsy and microscopic examination of organ samples were carried on animals dying during the study or were killed at the end of the study. Water intake was comparable in both control and methenamine treated test groups throughout the study. Body weights showed no significant differences between controls and methenamine treated groups. At the end of the second year 84% of survivors were noted in methenamine-treated and untreated animals. In

all methenamine treated rats a yellow coloration of the coat was observed. At necropsy and microscopic examination no specific pathological lesions related to methenamine treatment were observed in rats which died during the study or were sacrificed at the end of the test. Based on the results of the study, 1.0% (calculated intake 2.0-1.5 g/kg bw/d in males and 2.5-2.0 g/kg bw/d in females) methenamine was established as no-toxic-effect-level ($NOAEL_{sys}$) for outbred Wistar rats (Della Porta et al., 1968).

Mouse

30- or 60-week treatment period

Methenamine was tested in groups of male and female mice of three strains: CTM, outbred; C3hf/Dp, inbred; and SWR/Dp, inbred. Groups of male and female CTM mice (10 weeks old) received 0, 0.5, 1.0, or 5.0% methenamine in the drinking water for 30 or 60 weeks. The dosage regime and group size employed for CTM mice are summarized in table 4.4

Table 4.4: Dosage regime for methenamine in CTM mice

Concentration In drinking water (%)	Dose, calculated daily intake (g/kg bw/d)	No. of animals (males/females)	Duration of treatment (weeks)
0.0	0.0	99/100	60
0.5	1.25	50/50	60
1.0	2.5	96/102	60
5.0	12.5	29/50	30

In the SWR/Dp mice (7 weeks old) the control group consisted of 45 males and 30 females. 29 male and 27 female mice received 1.0% methenamine in drinking water for 60 weeks (calculated daily intake of 2.5 g/kg bw/d in either sex). In the C3Hf mice (5 weeks old) 30 males and 63 females received water only, and 49 males and 44 females received 1.0% methenamine in the drinking water over a period of 60 weeks (calculated daily intake of 2.5 g/kg bw/d in either sex). After termination of treatment, mice were observed up to 100 weeks of age. There were no data on hematology and clinical biochemistry. Necropsy was performed on all animals that died on study or were killed at termination of the study. Organ samples (no data for the list) and all gross lesions taken at necropsy were evaluated microscopically.

Water intake was similar in both control and methenamine treated groups throughout the study. Body weight gain showed no significant differences between control and methenamine treated SWR and C3Hf strain groups. Treatment of CTM mice with 5.0% (12.5 g/kg bw/d) methenamine for 30 weeks resulted in a significant reduction in survival rates and slight reduction of growth in the surviving animals. Slight retardation of growth was also seen in SWR mice treated with 1.0% (2.5 g/kg bw/d) methenamine. The effect on growth in SWR

mice was very small, not statistically significant, and no corroborating findings were noted at necropsy and microscopy. In addition there were no methenamine-related gross and microscopic findings in mice of all tested strains which died during or were killed at the end of the experiment. Therefore, for mice a $NOAEL_{sys}$ of 2.5 g/kg bw/d methenamine in either sex was obtained (Della Porta et al., 1968).

Dermal

Rabbit

There are limited data to assess toxic effects of methenamine as a result of repeated dermal exposure. Zondlo (1992) cited a subchronic toxicity study by dermal administration on rabbits to methenamine of COLIPA (1989). A full report of this study was not submitted. The following summary data are cited:

Two groups of rabbits (strain unspecified), 6 males per group, were used in this repeated dose dermal toxicity test. Two ml of 0.20% methenamine (equivalent to 1.3 mg/kg bw/d assuming a mean body weight of 3 kg) were applied in distilled water to one group of rabbits; the other group served as a control. The methenamine treated animals received applications of test solution during 5 days a week for a period of 6 weeks; the applications were given without occlusive patches. General behavior, hair growth, and body weight gain were comparable in both the controls and methenamine treated groups. No erythema, edema, scratching, or variation of the cutaneous fold were observed in the methenamine treated animals given approximately 1.3 mg/kg bw/d methenamine when compared to the controls.

Inhalation

No data available.

Other routes

Subcutaneous injections (rat and mouse)

20 male and 20 female outbred Wistar rats, and 39 male and 44 female 10-day-old CTM mice were treated by subcutaneous injections with methenamine (commercial grade purity) as a 30% aqueous solution on 5 alternate days. Each animal was treated subcutaneously with a total dose of 25 g/kg methenamine (equivalent to 50 mg/kg bw/d). After the dosing period, all animals were observed for the rest of their lives. Animals were inspected daily and weighed every 2 weeks. Water intake was determined periodically (no further information). Necropsy and microscopic examination (no list of organs and tissues available) was carried out on animals dying during the study or killed at the end of the experiment. After the treatment period no toxicologically significant effects on animal survival, behaviour, and body weight gain were noted for either rats or mice. There were no changes in macroscopic and

microscopic examination that were considered as a treatment related effect (Della Porta et al., 1968).

Intramuscular injections (rat)

Each of 5 male and 5 female BD (cPah) rats received intramuscular injections of 0, or 200 mg/d methenamine for 90 days (about 800 mg/kg bw/d in males and 1100 mg/kg bw/d in females, calculated on an assumed mean body weight of 250 g for male rats and 180 g for females, purity unspecified). There were no data on hematology and clinical biochemistry. No differences from controls in behaviour, body weight gain and feed consumption in rats of both sexes were observed. The only clinical sign observed in animals of both sexes treated with methenamine was a citrus-yellow discoloration of the hair coat. No treatment-related macroscopic or histopathological findings were available. Based on the results of this study, about 800 mg/kg bw/d in males and 1100 mg/kg bw/d in females are considered to be the no-observed-adverse-effect-level ($NOAEL_{sys}$) for methenamine by intramuscular injection for 90 days (Brendel, 1964).

Summary of animal toxicity data after repeated exposure to methenamine

There are no oral repeated dose toxicity studies with a full range of parameters to be examined according to the current regulatory requirements (EEC methods, B.7, B.9, B.26, B.30). Nevertheless, there are a number of older diet, gavage and drinking water studies in several animal species. None of these studies provided data on hematology and clinical chemistry; data on histopathology were limited. However a number of these repeated dose toxicity studies by oral administration (gavage, feed, drinking water) showed that methenamine did not cause any toxic effects in experimental animals up to and including 2.5 g/kg bw/d. All in-life parameters, which included body weight gain, food consumption, and survival, were unaffected by exposure to methenamine. Similarly, postmortem analyses, which included organ weights, gross pathology and histopathology, were unchanged following exposure to methenamine. The only clinical observation in studies with rats was a yellow staining of the perineal hair in some cases which is of no toxicological relevance. The yellow coloration of the fur observed in treated rats was reported by Brendel (1964), both after repeated feeding and after intramuscular injection of methenamine. Such yellow discoloration of the fur was only noted in rats and not in other experimental animals studied. This fur discoloration in methenamine treated rats may be a consequence of a reaction between formaldehyde in the urine and kynurenine, a normal constituent in the rat hair (Kewitz, 1966).

In a subchronic dermal toxicity study in rabbits using an aqueous methenamine solution at a concentration of 0.20% (equivalent to 1.3 mg/kg bw/d) no systemic or local effects were noted in animals of both sexes (COLIPA, 1989, cited by Zondlo, 1992).

There were no animal studies on repeated dose toxicity of methenamine after inhalation.

Human data:

Information on repeated human exposure to methenamine apart from therapeutic use is small. There are a limited number of available studies on the effects of methenamine on man following occupational exposure. Methenamine as solid, in solution and as vapour irritates human skin and mucous membranes and causes skin sensitization (cf. also 4.1.2.3 and 4.1.2.5). However,, the available data from occupational exposure to methenamine were generally unsuitable for determining the potential toxicity of methenamine in humans. Workers were usually exposed to mixtures consisting of several compounds including methenamine, and methenamine exposure levels were usually not reported. Therefore, the observed effects in workers in the rubber production and in foundries exposed to such mixtures could not be clearly attributed to methenamine exposures.

A cross-sectional study was performed with 33 employees of a methenamine producing plant to investigate the health effects of methenamine on the airways and the skin of the workers (Merget et al., 1999). Sixteen employees with no or only occasional low exposure to the substance served as controls. The exposed group consisted of 17 employees with exposure to far higher concentrations (baggers, shiftleaders, and executive staff). In addition, 4 out of 5 employees who had left the production for medical reasons during the last 10 years were included in the study. For each worker, anamnesis data were recorded and a physical examination of the skin and lungs was performed. In addition, total and specific IgE to four environmental allergens was determined, lung function and bronchial hyperresponsiveness were assessed, and skin prick tests and patch tests were performed with known sensitizing substances as well as with methenamine.

Inhalable dust, respirable dust, methenamine, formaldehyde, and ammonia were measured at different sites of the plant and/or in personal air space in order to assess the exposure levels. The concentrations of dust and chemicals were in the range of 0.2-2.6 mg/m^3. Geometric mean methenamine concentrations as determined by personal sampling were 0.3 mg/m^3 in shiftleaders and 0.6 mg/m^3 in baggers.

Irritant dermatitis of the hands, predominantly on the palmar parts, was observed in all highly exposed workers, but also, to a lower extent, in two controls. No other differences were found between the exposed and the control group.

Two workers in the exposed group and one in the control group had work-related symptoms. One of the two exposed workers reported shortness of breath, rhinoconjunctivitis and dermatitis of the hands, face and neck, which occurred after “accidents with high formaldehyde exposure”. The second exposed worker had pre-existing hay fever and seasonal asthma and gave a history of work-related shortness of breath and rhinitis. However, his lung function was normal and no bronchial hyperresponsiveness was observed. One worker of the control group reported work-related conjunctivitis, probably due to long-lasting computer work. In the skin prick tests and the patch tests, no sensitization to methenamine was found in either exposed or control workers.

Methenamine patch tests were positive in two ex-workers (former baggers) who reported contact dermatitis of the hands or generalized eczema and conjuctivitis within 2 weeks or 7 month of exposure. Two former workers with negative patch tests, experienced eczema of the neck “shortly” after the exposure and recurrent swelling of eyelids and wrists one year after the exposure, respectively. At the time of the study they both presented with eczema, although improved. Occupational asthma due to methenamine was not diagnosed in this study. (Merget et al., 1999; cf. also 4.1.2.5).

Seven workers in the lacquer or plastics industries who had worked with epoxy resins, plastics, or paint developed asthma and other allergic symptoms e.g. allergic coryza (nasal catarrh), contact dermatitis, or allergic conjunctivitis. At the workplace these employees were exposed to a variety of chemical compounds. An intracutaneous skin test with 0.02 ml of a 1:100 dilution of methenamine gave positive reactions in all tested workers. The positive reaction was characterized by immediate wheal formation. In a provocative test the workers were inhaling an aerosol of the lacquer product and showed either wheezing, a feeling of heaviness on the chest, or severe asthma, allergic coryza, or skin manifestations of allergy. Some of the workers also had positive reactions to ethylenediamine in both tests (Gelfand, 1963).

An epidemiological study investigated acute and chronic skin and respiratory problems of workers in the rubber industry who were exposed to a phenol-formaldehyde type resin. The study was carried out in a tire manufacturing plant using a methenamine-resorcinol resin system. The subjects of the study were intermittently or continuously exposed to a methenamine-resorcinol mixture (which comprised 2-3% of the total rubber mix) as well as to reaction products therefrom, which presumably included, inter alia, formaldehyde, ammonia, cyanides and curing agents. Acute and chronic symptoms of skin and respiratory problems were assessed by questionnaire. Smoking and drinking habits were considered. Baseline lung function tests were performed on the concerned workers before and after exposure as well as on a group of workers randomly selected from the total staff. Furthermore, measurements of respirable particulates were made for all workersand their respective environments. The exposure situation was characterized by analysis of respirable particulates (cut-off: 10 μm) and total particulates as well as formaldehyde, ammonia, resorcinol, and hydrocyanide. However, methenamine was not analyzed directly.

Personal loads of respirable particulates were less than 0.5 mg/m^3; environmental, respirable particulates concentrations in the work areas were about half of the personal loads and approximately 1/5 of total particulates concentrations.

Rubber workers exposed to methenamine-resorcinol-mixtures reported strong acute symptoms and significant reductions in expiratory flow rates at low lung volumes. Flow rates of smokers were stronger reduced than those of non-smokers. The greatest reduction in ventilation capacity was associated with methenamine-resorcinol exposure. The specific agents causing the functional losses are unknown; however, respirable particulates were related to functional losses in the methenamine-resorcinol exposed group, with no significant overall difference in environmental measurements between the other groups of the study. There was essentially no difference in baseline lung function values between exposure groups. Itching, skin rash, greater difficulty in breathing at work, chest tightness, burning eyes, running nose, burning sensation in the heart region, persistent cough and phlegm were acute symptoms associated with work. The acute effects seen in methenamine-resorcinol exposed workers are comparable to those alterations found in other industries, e.g. coal miners and textile workers. In summary, no direct causal relationship could be drawn between any responsible agent and adverse effects (Gamble, 1976).

Several previous health reports of foundry workers have shown an excessive prevalence of respiratory diseases. To evaluate the nature and the frequency of respiratory symptoms and to assess ventilation function a survey was carried out in a steel foundry specialised in producing castings for heavy industry and rolling stock. After completion of the survey various environmental contaminants were measured. The conditions appeared to be representative of

those existing at the time the lung function tests were performed.. Foundry workers were exposed to numerous fumes or vapours from various molding processes at their workplaces, including the Furane, Isocur, Shell, carbon dioxide, and oil sand systems. The type and frequency of respiratory symptoms were assessed by questionnaires. Wheeze and other respiratory tract symptoms like cough, nasal and eye irritation were often reported relating to environmental exposure at work, particularly from the Shell process which uses a phenol-formaldehyde resin and methenamine as a catalyst. However, a definitive allocation to a specific process was not possible as the workers circulated in the foundry. Ventilation function examined from Monday to Friday of one week showed small and inconsistent changes. Ventilation function recorded before work on Monday morning showed no evidence of chronic airway obstruction in any group. Most environmental measurements of chemical contaminants were below the legal limits, except in the general foundry, where furfuryl alcohol was detected in air at concentrations up to 50 ppm and formaldehyde at 4 ppm, respectively. Exposure levels to methenamine were not determined at these measurements. In summary, there were no significant differences in the frequencies of chronic cough and breathlessness among the different groups; furthermore, no clear causal relationship could be established between the observed adverse effects and any particular causative agent. The onset of symptoms in relation to the exposure to various fumes and vapours (mixed exposure to methenamine together with other well known compounds such as formaldehyde) suggests that both irritant and hypersensitivity mechanisms might be induced (Low and Mitchell, 1985).

Methenamine has been used for years as an orally given therapeutic substance especially as urinary antibacterial-antiseptic drug in humans as well as for long-term prophylaxis of urinary tract infections in patients who are at risk for bacterial reinfections. The bactericidal effect of methenamine has been attributed to its slow hydrolysis in the urine to ammonia and formaldehyde. This hydrolysis is both pH- and time-dependent. For methenamine to be effective, an acidic urine with a pH <5.5 must be maintained. The combination of methenamine with acid salts (hippurate and mandelate) helps to maintain the urinary pH in the desired range. The effectiveness of methenamine depends on an adequately maintained urine concentration of formaldehyde that is easily altered by an increase in pH of the urine, an increased fluid intake and high urine output, and the duration that urine is retained in the bladder (Hanselaar, 1983; Pischel, 1988; cf. 4.1.2.1).

Adverse effects have been reported in less than 3.5 % of patients receiving methenamine or its salts as drugs. The most frequent adverse effect observed was gastrointestinal disturbance, comprising of nausea, vomiting, diarrhoea, abdominal cramps, and anorexia. Rarely, hypersensitivity reactions such as rash, pruritus, urticaria, and stomatitis have occurred. Other, less frequently reported, side effects are headache, dyspnoea, generalized oedema, tinnitus, muscle cramps, dysuria, and microscopic or gross haematuria (McEvoy, 1997 – quoted from HSDB 2000; Martindale, 2005).

It is known that high therapeutic doses of 8 g methenamine/d (corresponding to ca. 114 mg/kg bw/d based on a body weight of 70) administered for 3 to 4 weeks induced urological abnormalities such as bladder irritation, painful and frequent micturition, albuminuria and hematuria. Singular side effects reported were gingivitis, anorexia, headache, and generalized edema (Goodman and Gilman, 1975; Mon. 144, 1988).

No complications were observed in patients receiving methenamine in the standard treatment for acute cystitis in adults at dose levels of 2 to 4 g/d (corresponding to about 28 to 57 mg/kg

bw/d based on a body weight of 70 kg) for a 7- to 10-day course up to four weeks. Methenamine is also used for long-term suppressive therapy or for prevention of recurrent urinary infections (prophylaxis) because acquired resistance does not appear to develop. The usual oral dose of methenamine (methenamine hippurate or methenamine mandelate) for long-term treatment (6 months or longer) is 2-4 x 1 g/d (corresponding to ca. 28-57 mg/kg bw/d based on a body weight of 70 kg) No relevant side effects from the treatment with this dose level were reported (Goodman and Gilman, 1975; Martindale, 2005).

Summary of human toxicity data after repeated exposure to methenamine

Methenamine is widely used as an accelerator and a hardener in the rubber and plastics industries. However, the number of available studies on the effects of methenamine on man following occupational exposure is limited. Toxic effects in humans at the workplace have only been reported after repeated exposure to mixtures of several compounds, including methenamine. Workers in production plants, in the lacquer and plastics industries, in tire manufacturing plants and in foundries can be exposed to methenamine by inhalation or skin contact. In all these workplaces, the workers are also exposed to other chemicals (e.g. formaldehyde, ammonia, resorcinol, phenol, furfuryl alcohol, cyanides, epoxy resins, curing agents). Therefore, the available occupational exposure studies were not adequately designed to specifically address the nature and origin of symptoms occurring in rubber and foundry workers, or to establish a plausible dose-response relationship relating to a single substance. Considering the lack of information on the exact exposure situation, especially the actual levels of methenamine exposure, it is not possible to make qualitative assessments of the observed effects in relation to methenamine exposure alone. Lung function measurements in one of the studies revealed significant reductions in expiratory flow rates at low lung volumes. In another study, an intracutaneous skin test with methenamine gave positive reactions in all workers, and a provocative inhalation test with an aerosol of a lacquer product revealed allergic reactions from the lungs, the nose or the skin. Since the early use of methenamine in the rubber and resins industries, however, increased incidences of wheeze and further respiratory tract symptoms like cough, and nasal and eye irritation were reported in workers who were simultaneously exposed to methenamine and other chemicals such as resorcinol.

No adverse effects were observed in patients receiving methenamine for long-term prophylaxis or therapy especially as urinary antibacterial-antiseptic substance at dose levels of 2 to 4 g/d (corresponding to ca. 28 to 57 mg/kg bw/d) for several weeks weeks or months. However, with a higher dose of 8 g/d (corresponding to ca. 114 mg/kg bw/d) over 3 to 4 weeks clinical symptoms such as bladder irritation, painful and frequent micturition, albuminuria and haematuria were reported. Albuminuria or hematuria were not observed in experimental animals.

No observed adverse effect level (NOAEL)

Animal data

Oral administration

Although no repeated dose toxicity studies in experimental animals by oral administration are available which examined a full range of parameters (corresponding to the current regulatory requirements of EEC methods B.7, B.9, B.26, or B.30), there is a number of older drinking water, diet and gavage studies. These studies can be used as support for a risk assessment in combination with data from observations in humans (see end of this section).

Thus, the available data are considered to be sufficiently acceptable with regard to the basic requirements as specified in Annex VIIA of Directive 67/548/EEC and permit the derivation of $NOAEL_{sys}$ for repeated-dose oral toxicity.

No specific organ toxicity was recorded after repeated oral administration of methenamine (by gavage, in feed or in drinking water) in several experimental animal species for different duration of exposure (subacute to chronic).

The systemic NOAEL values derived from animal studies with methenamine for different exposure durations are summarized in Table 4.5.

Table 4.5: Summary table: $NOAEL_{sys}$ values for methenamine derived from oral toxicity studies in experimental animals

Species/strain (m/f)	Exposure route	Exposure duration, frequency	$NOAEL_{sys}$ for relevant non-neoplastic effects	Reference
Rat/BD (cPah) (5m/5f)	gavage	90 days daily	m: 1280 mg/kg bw f: 1780 mg/kg bw/d	Brendel 1964
Rat/BD (cPah) (15m/15f)	gavage	333 days daily	m: 1130 mg/kg bw/d f: 1570 mg/kg bw	Brendel 1964
Rat/Wistar (16m/16f)	feed	Lifespan daily	m/f: 100 mg/kg bw/d	Natvig et al. 1971
Rat/Sprague-Dawley (15m/15f)	drinking water	50 weeks 5 d/wk	m: 80 mg/kg bw/d f: 100 mg/kg bw/d	Lijinsky and Taylor 1977
Rat/Wistar (48m/48f)	drinking water	104 weeks daily	m: 2000 mg/kg bw/d f: 2500 mg/kg bw/d	Della Porta et al. 1968
Mouse/CTM (96/102	drinking water	60 weeks daily	m/f: 2500 mg/kg bw	Della Porta et al. 1968
Mouse/SWR/Dp (45m/30f)	drinking water	60 weeks daily	m/f: 2500 mg/kg bw	Della Porta et al. 1968
Mouse/SWR/Dp; C3Hf (30m/63f)	drinking water	60 weeks daily	m/f: 2500 mg/kg bw	Della Porta et al. 1968
Cat/strain not specified (2m/3f)	feed	lifespan daily	m/f: 60.65 mg/kg bw/d	Kewitz 1966, unpuplished report

m: male; f: female; $NOAEL_{sys}$: No observed adverse effect level for systemic effects

The lowest dose level causing no adverse toxic effects in rats could be derived from a chronic oral administration of methenamine in drinking water to Sprague-Dawley rats. At the only

tested dose level of 0.1% methenamine (equivalent to 80 mg/kg bw/d in males and 100 mg/kg bw/d in females) no effects on body weight gain, behaviour, macroscopic or microscopic findings were observed (Lijinsky and Taylor, 1977).

50-week oral (drinking water)/Sprague-Dawley rat

$NOAEL_{sys}$ 80 mg/kg bw/d in males and

100 mg/kg bw/d in females (Lijinsky and Taylor, 1977)

In a further long-term drinking water study in Wistar rats that was equal in test design and quality to the above-mentioned study the administration of methenamine at 2 g/kg bw/d in males and 2.5 g/kg bw/d in females for 104 weeks was tolerated without adverse effects. There was no evidence of toxic effects on the general behavior and the main organs (Della Porta et al., 1968).

104-week oral (drinking water)/Wistar rat

$NOAEL_{sys}$ 2 g/kg bw/d in males and

2.5 g/kg bw/d in females (Della Porta et al., 1968)

In a lifetime diet study in Wistar rats, in which only one dose (0.16%, equivalent to approximately to about 100 mg/kg bw/d in both sexes) was tested, no significant differences between control and test group with respect to body weight, organ weight, histopathological findings, life-span and causes of death were seen (Natvig et al., 1971).

Lifetime study oral (diet)/Wistar rat

$NOAEL_{sys}$ 100 mg/kg bw/d in males and females (Natvig et al., 1971)

In a comparative investigation oral methenamine administrations of ca. 1130 mg/kg bw/d in males and 1570 mg/kg bw/d in female BD (cPah) rats for 333 days showed no differences in macroscopic lesions in the main organs of test and control groups (Brendel, 1964).

333-day study oral (gavage)/ BD (cPah) rats

$NOAEL_{sys}$ 1130 mg/kg bw/d in males and

1570 mg/kg bw/d in females (Brendel, 1964).

In an oral toxicity study given methenamine in the drinking water for 60 weeks and following a subsequent treatment-free period male and female mice of the CTM, SWR/Dp and C3Hf strains showed no methenamine-related effects at 2.5 g/kg bw/d (Della Porta et al., 1968).

60-week oral (drinking water)/ CTM, SWR/Dp and C3Hf mouse

$NOAEL_{sys}$ 2.5 g/kg bw/d (Della Porta et al., 1968).

No treatment-related effects were found in food consumption, body weight gain, or behavior in male and female cats (strain unspecified) receiving methenamine in feed at a dose of 60.65 mg/kg bw/ up to two years (Kewitz, 1966, unpublished report).

106 week oral (feed)/cats (strain unspecified)

$NOAEL_{sys}$ 60.65 mg/kg bw/d (Kewitz, 1966, unpublished report)

Dermal exposure

There are limited data to assess toxic effects of methenamine as a result of repeated dermal exposure. Zondlo (1992) cited one repeated dose toxicity study by dermal administration of methenamine in rabbits initiated by COLIPA (1989). A full report of this study was not submitted. Data were presented in summary form, only. No systemic and local effects were noted in this subchronic dermal toxicity study in rabbits using an aqueous methenamine solution at a concentration of 0.20% (equivalent to 1.3 mg/kg bw/d).

6-week dermal (5 days/week)/rabbit (strain unspecified)

$NOAEL_{sys}$ 1.3 mg/kg bw/d (COLIPA, 1989, cited by Zondlo, 1992)

Inhalation

No studies are available to assess toxicity after repeated inhalation exposure.

Human data:

From the use of methenamine for long-term therapy or the prevention of recurrent urinary infections in man it was known that dose levels of 2 to 4 g/d produced no harmful reactions or complications (Goodman and Gilman, 1975; Martindale, 2005). However, therapeutic doses of 8 g/d for 3 to 4 weeks produced side effects such as bladder irritation, painful and frequent micturition, albuminuria and hematuria (Goodman and Gilman, 1975; Mon. 144, 1988).

Dose level causing no toxic effects in man: 2 to 4 g/d, equivalent to ca. 28 to 57 mg/kg bw/d (Goodman and Gilman, 1975; Martindale, 2005).

In summary, the most sensitive $NOAEL_{sys}$ for systemic effects was derived in man. The NOAEL of 4 g/d (57 mg/kg bw/d based on a body weight of 70 kg person) in man (Goodman and Gilman, 1975; Martindale, 2005) is derived from decades of long experience with methenamine as a therapeutic substance.

Man	$NOAEL_{sys}$ 57 mg/kg bw/d

Classification

On the basis of the data submitted, classification of methenamine as harmful and labelling with Xn, R 48/22 (Harmful: danger of serious damage to health by prolonged exposure if swallowed) according to the criteria given in Directive 67/548/EEC does not seem necessary.

4.1.2.8 Mutagenicity

In vitro assays with bacteria

In the bacterial gene mutation assay weak positive effects with and without S-9 mix are described for tester strains TA 97, TA 98 and TA 100 (approx. 2-fold increases compared to control values) only in high concentrations from 10 000 µg/plate upwards (Zeiger et al., 1992). The approximately 2-fold increases of the mutation rates (compared to the control value) were observed only at clearly higher concentrations than 5000 µg/plate, the maximum test concentration recommended by the guideline (Shimizu et al., 1985). For tester strains TA 1535, TA 1537, TA 1538 and WP2uvrA up to 10 000 µg/plate negative results were found with and without S-9 mix (Andrews et al., 1980; Crebelli et al., 1984).

In vitro assays with mammalian cells

Girmanova et al. (1991) reported on a positive chromosomal aberration assay with V79 cells: In the highest analysable concentration of 10 mmol/l 7% aberrant cells (without gaps) were induced compared to 2% in control cultures. Higher doses were strongly cytotoxic. Only one experiment without S-9 mix was done. In the same publication slightly increased SCE frequencies were described after treatment of V79 cells with 10 and 50 mmol/l methenamine.

In a poorly documented chromosomal aberration assay with HeLa cells negative results were found up to concentrations of 1 mmol/l; higher tested doses induced strong cytotoxic effects (Baldermann et al., 1967). Information on the use of S9 is not given.

Dooley et al. (1995) reported in an abstract without detailed data on a negative mouse lymphoma assay with methenamine under addition of formaldehyde dehydrogenase and NAD^+ to the test system.

In vivo assays with mammals

Two in vivo chromosomal aberration tests with mouse bone marrow cells were negative (Vujosevic et al. 1986). An in-vivo chromosomal aberration test with mouse bone marrow cells led to a negative result after single oral doses up to 618 mg/kg (corresponding to 1/3 of LD_{50}-value). Sampling times were 6 h, 12 h, and 24 h after single treatments. Another in vivo chromosomal aberration test with mouse bone marrow cells led also to a negative result after repeated oral doses. Doses up to 618 mg/kg bw were given five times with intervals of 24 h; sampling time was 6 h after last administration.No information about clinical symptoms or cytotoxic effects is given by the authors. However, from the toxicokinetic data available it can be concluded that the substance was available at the target organ (see section 4.1.2.1).

A dominant lethal assay with mice led to a negative result after single i.p. doses of up to 10 000 mg/kg methenamine. A second trial, in which oral doses of 25 000 mg/kg (maximum tolerated dose) were administered, is not valid, because of higher frequencies of live implants in treated animals than in control animals (Baldermann et al., 1967) No psotive control substances were included.

Conclusion:

Methenamine was weakly positive in bacterial gene mutation assays at extremely high concentrations and in an in vitro chromosomal aberration assay. Due to these positive tests the substance seems to have a low mutagenic potential for bacteria and mammalian cells in culture. The negative in vivo chromosomal aberration tests and the negative dominant lethal test indicate that this potential is unlikely to be expressed in germ cells.

4.1.2.9 Carcinogenicity

Animal data

There are no carcinogenicity studies available in experimental animals according to the current criteria for the testing of carcinogenicity by oral, inhalation, or dermal application route. Some publications review long-term/lifetime studies performed to determine the effect of lifetime administration of methenamine on neoplasm development and life span of experimental animals or other selected questions. The test procedures of the presented studies are in accordance with generally accepted scientific standards, however, differ in some respects from the published guidelines. Significant study deficiencies were: size of experimental groups, only one dose level tested, range of organ weight assessment and histopathology. Nevertheless, the data submitted are considered useful in assessing the carcinogenic potential of methenamine. In long-term oral studies in experimental animals there was no evidence of carcinogenic activity in rats and mice following high dosage of 2500 mg/kg bw/d methenamine after long-term treatment.

Several long-term studies with oral application (gavage, feed or drinking water) in rats and mice are also reported in section 4.1.2.6. (cf. for detailed test designs).

Oral

Gavage studies (rat)

333-day study

15 male and 15 female BD (cPah) rats were treated with a total dose of 95 g methenamine by gavage (purity unspecified) for 333 days. Assuming a mean body weight of 250 g for male rats and 180 g for female rats, the mean methenamine dose was ca. 1130 mg/kg bw/d for male and 1570 mg/kg bw/d for female rats. Except for citrus-yellow fur discolorations of varying intensities, no difference in macroscopic findings in organs or in body weight gain between experimental and control groups of both sexes were observed Neither substance-related organ changes nor tumours were reported of animals which died or were killed at the end of the study (Brendel, 1964).

Diet study (rat)

Lifetime study

To study the effects of a lifetime methenamine intake, 16 male and 16 female Wistar rats were given either 0 or 0.16% methenamine (equivalent to 0, or ca. 100 mg/kg bw/d in both sexes, based on a body weight of 420 g of male and 280 g of female rats and a mean daily consumption of 42 mg methenamine - commercial grade purity - in males and 29 mg in females) in a standard diet from weaning (two months old) to natural death. General health, behavior, and muscular activity tested in the revolving drum after 1, 3, 7 and 14 months showed no significant differences between control and test groups. Food consumption and body weight gain were similar in both control and test groups throughout the study. There were no significant differences in relative organ weight or average natural life. Causes of death of treated animals were comparable to those of the matched controls throughout the study. No methenamine-induced lesions and carcinogenic effects in males and females given about 100 mg/kg bw/d were reported. Tumor incidence in the methenamine-treated animals was not higher than that observed in control animals (Natvig et al., 1971).

Drinking water studies (rat and mouse)

Drinking water studies were performed in rats and mice of various strains. The objective of these studies was to determine the possible carcinogenic potential of methenamine when administered in drinking water for one year or longer. Methenamine (commercial grade purity) was administered to experimental animals for up to 104 weeks. Additionally, animals of both species and sexes were then observed for a subsequent treatment-free period of varying duration (e.g. until the end of the natural life).

Rat

50-week treatment period

0.1% methenamine was administered in drinking water to two groups of 15 male and 15 female 8-10 weeks old Sprague-Dawley rats. Each group received methenamine either with or without 0.2% sodium nitrite on 5 days/week for a period of 50 weeks. The animals were then observed for the rest of their lives or were killed due to moribund condition. Each animal received a total dose of 5 g methenamine over the 50 weeks treatment (equivalent to 80 mg/kg bw/d in males and 100 mg/kg bw/d in females, based on a body weight of 250 g in males and 200 g in females). There was no significant difference in the survival rate Tumours were neither induced by methenamine alone nor in combination with nitrite (Lijinsky and Taylor, 1977).

104-week treatment period

Groups of 48 male and 48 female outbred Wistar rats (10 weeks old) received 0, or 1.0% (calculated intake 2.0-1.5 g/kg bw/d in males and 2.5-2.0 g/kg bw/d in females) methenamine in drinking water for 104 weeks. After the termination of treatment rats were observed for the rest of their lives. No differences between treated and control animals were observed regarding water intake and body weight gain. An 84% survival rate was noted at the end of the second year in methenamine-treated and untreated control animals which were kept under lifetime observation. The incidence, severity, and distribution of macroscopic and microscopic findings did not differ among treated rats and controls. Furthermore, the incidences of observed tumors and the tumor types observed in rats were comparable in all methenamine-treated and control groups. The percentage of tumor-free animals was higher in the methenamine treated groups than in controls. In conclusion, long-term administration of 1.0% methenamine in the drinking water to outbred Wistar rats did not show tumorgenic changes (Della Porta et al., 1968).

Mouse

30- or 60-week treatment period

In long-term experiments for carcinogenicity in mice, outbred 10-week-old CTM mice, inbred 5-week-old C3hf/Dp mice, and inbred 7-week-old SWR/Dp mice were used. Groups of male and female mice of these strains received 0, 0.5, 1.0, or 5.0% methenamine in the drinking water for 30 or 60 weeks. The dosage regiment for methenamine and group size for mice in these studies are taken from the study reported under 4.1.2.6 and Table 4.4. After methenamine treatment ceased, mice were further observed a subsequent treatment-free period up to 100 weeks of age.

Water intake and body weight gain were similar in both controls and methenamine treated groups throughout the study. However, treatment of CTM mice with 12.5 g/kg bw/d methenamine for 30 weeks resulted in slight reductions in growth rate and survival. Slight retardation of growth was also seen in SWR mice treated with 2.5 g/kg bw/d methenamine. Similar incidences of malignant lymphomas and leukemia, mammary carcinomas, pulmonary adenomas, hepatomas, liver angioma and Harderian-gland tumors were found in both the methenamine-treated animals and control. No significant differences in total tumor incidence between methenamine-treated and untreated groups were reported. The percentage of tumor-free animals varied slightly in all strain groups. Overall, in the mouse studies, there were no significant differences in the total tumor incidences between the methenamine-treated groups and control groups (Della Porta et al., 1968).

Dermal

No data available.

Inhalation

No data available.

Other routes

Subcutaneous injections (rat and mouse)

Groups of 39 male and 44 female infant outbred CTM mice and 20 male and 20 female outbred Wistar rats were treated by repeated subcutaneous injections with a 30% aqueous solution of methenamine (commercial grade purity) on 5 alternate days starting on day 10 of age. Each rat and mouse was treated subcutaneously with a total dose of 25 g/kg methenamine (equivalent to 50 mg/kg bw/d). After termination of dosing, all animals were then observed for the rest of their lives. No methenamine-related findings were seen regarding growth, mortality rates, average lifetime and histopathological findings. The study showed no difference with respect to type and incidence of tumors between the groups (Della Porta et al., 1968).

Summary of animal carcinogenicity data after long-term, lifetime exposure

The existing long-term/lifetime studies on methenamine are not in accordance with current testing procedures as proposed by guidelines on carcinogenicity and/or combined chronic toxicity/carcinogenicity (EEC methods, B.32, B.33). However, the carcinogenicity of methenamine has been investigated in a number of long-term oral studies, involving a variety of strains of rats and mice. Overall, results of these studies did not demonstrate that methenamine is carcinogenic in experimental animals after treatment with dosages up to 2.5 g/kg bw/d (Brendel, 1964; Natvig et al., 1971; Della Porta, 1968; Lijinsky and Taylor, 1977).

In vitro data:

Cell transformation assay

A transformation assay using mycoplasma-free neonatal hamster kidney (BHK) cells was used to screen for carcinogenic potential of methenamine (commercial grade purity). The assay was performed following the method of Styles. Sterile distilled water served as both the solvent and negative control. The test was performed with metabolic activation, however, the toxicity and transforming activity of methenamine was not influenced by metabolic activation. In initial experiments, a concentration dose range of 0.025-250 µg/ml methenamine was used. A dose-dependent increase in the number of transformed colonies and a negligible toxic effect was observed. The concentration range was then increased to 1-10000 µg/ml. When the test cultures were compared to the non-exposed cultures, 80% of the cells survived the maximum concentration. A dose-dependent and significant increase in the

number of transformations was observed; transforming activity was observed at a nontoxic or a very weakly toxic concentration (Plesner and Hansen, 1983).

Summary of cell transformation tests

An increase in the transformation rate in Styles' cell transformation assay using BHK-21/cl.13 cells was observed after exposure to 1000 µg/ml methenamine. However, this test system is not validated and the methodology is insufficiently documented (Plesner and Hansen, 1983).

Human data:

Human data

There are health and mortality studies of humans exposed at their workplace to mixtures of several compounds with suspected carcinogenic potential (e.g. formaldehyde, ammonia, cyanides, carbon black, asbestos, benzene, various polycyclic aromatic hydrocarbons), which also included methenamine. Due to insufficient study quality the available studies do not allow to draw a conclusion on a causal relationship between cancer in humans and exposure to specific chemical substances. Workers, commonly employed for instance in steel or tire foundry or in rubber production, were usually exposed to methenamine contained in substance mixtures. Therefore, the observed increased incidence of tumors in workers could not be causally attributed specifically to exposure to methenamine.

In a cohort study, 13570 white male workers, who had worked in a rubber plant for at least 5 years and were exposed to methenamine combined with several other compounds were followed up to 36 years (from 1940 – 1976). Some of these compounds which are used as antioxidants and accelerators in the rubber making are suspected carcinogens. Mortality rates were compared to standardized rates of US white males. Cancer morbidity rates were also compared among persons who were employed in various work areas of the plant. Excess cases of specific cancers (observed/expected numbers) among workers in specific areas were identified and correlated to specific working areas. Expected cases were calculated on the basis of age-specific morbidity and mortality rates for employees that were not working in specifically affected areas and amounted to >10000 to 12545 individuals. The cohorts under study generally consisted of several hundred workers (ca. 250 to 2000, depending on working place, department considered, and duration of employment). No specific exposures were monitored or recorded and related to cancer frequencies. For almost all tumor types positive associations with certain working areas were identified, provided the duration of employment was at least 5 years. Among others the following results were obtained (number of cases with specific cancers among workers in specific work areas; observed/expected): stomach and intestine: rubber making (30/14.1); lung: tire curing (31/14.1); fuel cells and/or deicers (46/29.1); bladder: chemical plant (6/2.4), and tire building (16/10.7); skin cancer: tire assembly (12/1.9); brain cancer: tire assembly (8/2.0); lymphatic cancer: tire building (8/3.2); and leukemia: calendering (8/2.2), tire curing (8/2.6), tire building (12/17.5), elevators (4/1.4), tubes (4/1.6), and rubber fabrices (4/1.1). Due to the complex nature of the working environment the positive associations between the increase in cancer morbidity for workers in a rubber plants and the different working places could not be correlated to exposures to specific chemicals. Therefore, responsible compounds could not be identified (Monson and Fine, 1978).

Based on information of about 20067 personal data sheets of white male workers (up to the end of 1979) provided by the joint National Cancer Institute/Formaldehyde Institute (NCI/FI) cohort data, a retrospective evaluation was conducted. In this revision, previous key analyses were repeated by using data only for those workers whose duration of employment was one year or more. These workers represented 63.5% of the whole collective (12743 persons) and contributed 66.5% of 242 lung cancer deaths in the study. These cases were distributed over 10 plants. With a special program (OCMAP software), lung cancer rates for the white males in this cohort were calculated in consideration of plant, age, calendar time, and job type for several time-dependent formaldehyde exposures, including formaldehyde exposure in the presence of 12 selected co-exposures such as ammonia, antioxidants, asbestos, carbon black, dyelins/pigments, methenamine, melamine, particulates, phenol, plasticizers, ureal compounds, wood dust and a composite co-exposure involving antioxidants, methenamine, melamine, phenol and urea/urea compounds. Analysis of the internal cohort rates corroborates previous analyses of the NCI/FI cohort data in those significant positive associations were found between the risk of lung cancer and cumulative exposure to formaldehyde in the presence of several of the same co-exposures. However, based on the analysis of these data, it was not possible to associate a causal connection between occupational exposure to methenamine and lung cancer risk in humans (Marsh et al., 1992).

Another study was set up to investigate potential chronic health effects associated with molding in the foundry industry with mixed exposure to methenamine and other compounds including carbon monoxide, nitrogen oxides, hydrogen cyanide, ammonia, amines, aldehydes, phenols, benzene, benzoic acid, toluene, cresols, methane, ethylene, acetylene, and various polycyclic aromatic hydrocarbons (Hansen, 1991). For this purpose, a cohort of 632 male molders was followed through 10 years with regard to cause-specific mortality. Comparisons were made with another cohort of skilled workers. It was shown that the mortality from cancer was increased among the molders (standardized mortality ratio 152, 95% confidence interval 100-221), mainly because of an excess number of deaths from bladder cancer (standardized mortality ratio 896, 95% confidence interval 329-1949). It was suggested that bladder carcinogens may be formed during certain processes of molding.. In addition, phenols, cresols, and aldehydes in the foundry work atmosphere were reported to act as tumor promoters. Due to the fact that workers were usually exposed to mixtures of several agents including methenamine, the observations in workers exposed to such mixtures in the environment could not be clearly attributed to exposures to methenamine. Consequently, no conclusion can be drawn regarding a possible causal association between exposure to methenamine and/or several other compounds or particles and cancer.

Summary of epidemiological studies among workers

Data on humans occupationally exposed to methenamine alone for a long time are not available. Workers in the steel foundry and in tire and rubber industries were exposed to mixtures of chemicals including methenamine. Considering the lack of important details in the evaluation of actual occupational exposure (e.g. frequency and duration of potential exposure or contact), measurements of methenamine concentrations in the blood, urine, exhaled breath, or other biological media from exposed workers, it was not possible to link observed effects in these workers to methenamine alone. However, health studies of workers in the steel foundry, and tire and rubber industries revealed an increase in mortality from cancer mainly because of an excess number of deaths from lung and bladder cancer. Because methenamine is a compound within mixtures of substances which workers were exposed to, it cannot be established whether the increased cancer mortality in these workers was associated

to the exposure to methenamine in particular. Several compounds which are used in rubber making or in the working process of steel foundry are suspected to be carcinogens.

In conclusion, the above-mentioned data and mortality studies available did not provide sufficient evidence for a causal association regarding an occupational methenamine exposure and cancer in humans.

Therapeutic use

From use of methenamine for long-term therapy or the prevention of recurrent urinary infections in humans it is known that dose levels of 2 to 4 g/d produced no harmful reactions or complications (Goodman and Gilman, 1975; Martindale, 2005). Adverse effects have been reported in less than 3.5 % of patients receiving methenamine or its salts as a drug (cf. 4.1.2.6 for details). With respect to the extensive use of the substance as a drug there is no information available on the formation of tumours in the urinary tract in humans.

Concern from mutagenicity data

Methenamine was weakly positive in bacterial gene mutation assays and in a chromosomal aberration assay at high concentrations. Due to these positive tests the substance seems to have a low mutagenic potential for bacteria and mammalian cells in culture. The negative in vivo chromosomal aberration test and the negative dominant lethal test indicate that this potential is unlikely to be expressed in vivo.

Other information

As described in 4.1.2.1, formaldehyde is formed as product of hydrolytic cleavage of methenamine, which is strongly dependent on acidic pH values. Therefore, formaldehyde formation is only relevant after oral administration as the pH of the stomach is acidic, and the amount formed will be dependent on residence time and stomach contents as well as pH. Further down the gastrointestinal tract, the pH is neutral with nearly no formation of formaldehyde. It may also be produced in the kidneys after therapeutic use of methenamine. With respect to the genotoxic potential of formaldehyde the question will be considered whether formation of tumours had been observed in the urinary tract of animals after administration of formaldehyde.

Upon oral ingestion, formaldehyde can be absorbed into the bloodstream, where it is converted to formic acid within 90 seconds. High concentrations of formic acid can rapidly necrose cells in the liver, kidneys, heart and brain. The half-life of formic acid is reported to be 90 min. Formic acid can be excreted through the kidney as sodium salt or is further oxidised to carbon dioxide and water (cf. Pandey et al., 2000).

Oral treatment of rats with formaldehyde (200 mg/kg bw) demonstrated induction of micronuclei and nuclear anomalies in stomach, duodenum, ileum and colon as compared to untreated controls (Migliore et al., 1989). The observed effects were strongest in the stomach. Other sites of the gastrointestinal tract were clearly positive but to a lesser extent with effects declining with distance from the stomach. These data suggest that formaldehyde not only

causes nuclear damage at the site of application (local genotoxicity), but may also be active at more distant sites.

However, in a valid cancer study in Wistar rats with a comparable study design as required by OECD TG 453 no increased tumor incidences have been detected in any organ (Til et al., 1989). Groups of 70 males and females were administered to drinking water containing formaldehyde adjusted to achieve target intakes of 0, 5, 25 and 125 mg/kg bw/d for up to 2 years (mean doses were 1.2, 15, or 82 mg/kg bw/d for males and 1.8, 21 or 109 mg/kg/bw/d for females). More than 30 organs/tissues were examined by histopathology: data on non-neoplastic and neoplastic effects were recorded and supplemented by parameters on haematology, clinical chemistry and urinalysis.

From this data it is concluded that the formation of formaldehyde due to the pH dependent cleavage of methenamine in slightly acidic body compartments should be of no concern with respect to carcinogenicity.

Conclusion:

At present the human data did not provide any conclusive information regarding the presence of a causal association between methenamine exposure and cancer in humans. There are some reports which describe findings on human health and an excess number of deaths from lung and bladder cancer on occupationally exposed workers in the steel foundry, tire and rubber industries. However, the results from these retrospective and prospective epidemiology reports did not show clear evidence of carcinogenic activity in humans due to exposure to methenamine as one of the compounds at the workplace in production and in the working processes. Because the workers were exposed to mixtures of chemicals consisted of several compounds with suspected carcinogenicity properties.

Long-term and/or lifetime studies in experimental animals did not demonstrate that methenamine is carcinogenic in rats and mice following high oral dosages up to and including 2.5 g/kg bw/d.

There were cell transformation data from one study. For methenamine an increase in the transformation rate in Styles' cell transformation assay using BHK-21/cl.13 cells was observed after exposure to 1000 µg/ml. However, this test system is not validated and the methodology was insufficiently documented. This study does not contribute to the overall assessment of the carcinogenic potential of methenamine.

Taking into account the negative results from in vivo genotoxicity testing, it is concluded that methenamine has not been considered to be carcinogenic for experimental animals.

Overall, a conclusion of evidence suggesting lack of carcinogenicity in humans is inevitably limited to the special conditions and levels of exposure and length of observation covered by the available health and mortality studies of occupationally exposed humans. However, studies in experimental animals involving two species (rat and mouse) are available which have shown that, within the limits of the test used, high oral doses of methenamine did not induce tumors in either rats or mice. Currently, the available data of methenamine are insufficient to justify the evaluation as a human carcinogen according to the EEC criteria for classification and labelling requirements for dangerous substances (EEC Directive 2001/59/EEC, Annex VI of the Directive 67/548/EEC). Therefore, there is no need for classification and labelling of methenamine as a carcinogen.

4.1.2.10 Toxicity for reproduction

Animal data

Fertility impairment

Guideline-conform generation studies, respectively fertility studies on methenamine are not available. From two older studies of restricted value only limited information can be obtained for hazard assessment with respect to reproduction.

An investigation on reproduction, which is poorly documented, was incorporated into a lifetime feeding study on Wistar rats which had received a standard diet to which 0.16% methenamine had been added (Natvig et al., 1971). The exposed group consumed about 100 mg/kg/day of methenamine. After three months of exposure, the 16 males and 16 females of the experimental group were inbred. From the resulting F1 generation another 16 males and 16 females were fed from weaning on to the same diet as their parents. Only a few parameters were evaluated and only scarce data were given as results: the report states, that in comparison to the controls no differences for average litter size were found, and that for the F1 generation no significant differences were found for mean body weights recorded at 7, 15, and 18 weeks of age and for relative organ weights (liver, kidney, adrenals, gonads) evaluated after termination at 18 weeks of age.

In a further study on transplacental toxicity and carcinogenesis with Wistar rats (Della Porta et al., 1970), the outcome of the exposure of animals to methenamine via drinking water was followed up in two independent experiments for one and for three successive generations.

In the first experiment 12 females and 6 males were given 1% methenamine in drinking water (daily intake of approximately 1.5-2 g/kg bw/d for males and of 2-2.5 g/kg bw/d for females) during two weeks before mating. For the females the treatment continued during pregnancy and lactation. A similar untreated group of 12 females and 6 males served as controls. Within 25-30 days after mating 11 treated females and 11 controls became pregnant and delivered 110, respectively 118 pups. After delivery the pups of the treated and the control group were culled to 8 offspring per litter (treated group 47 m/38 f, control group 37 m/46 f). After weaning these offspring on p.n. day 32, 24 of each sex were continued on 1% methenamine in drinking water up to the 20th week of age. In treated males up to postnatal week 9 and in treated females up to postnatal week 20, the body weights were significantly lower than those of controls. However, at the beginning of the postweaning weight determination period, the initial body weights of the offspring of treated dams were already lower than those of the offspring of the controls, indicating that growth deficits were already evident. After a post-treatment observation period of two weeks no differences were observed between treated and control groups in respect to organ weight and gross or microscopic alterations.

In a second experiment rats were given 1% methenamine in drinking water for three successive generations, up to the age of 40 weeks in the F1 and F2 groups and of 20 weeks for the F3 group, thereafter all groups were kept under observation up to week 130 of their lifetime. The parental generation (F0) group consisted of one male and two females that were given 1% methenamine in drinking water during four weeks before mating. The treatment of the females continued until two litters of ten pups each had been weaned. The descendant F1 groups consisted of 13 males and 7 females. The females were mated to 3 males of their group. One dam died during delivery while the remaining 6 dams gave birth to a total of 36

pups from which 10 died during lactation. The resulting F2 group consisted of 15 males and of 11 females. These females were mated to 4 males of their group and delivered a total of 99 pups from which only 12 males and 12 females were further raised to yield the F3 group. An additional testgroup of 5 females was run on 2% methenamine from mating through lactation. They delivered a total of 49 pups from which 16 animals per sex were continued on 2% methenamine for 50 weeks. All groups were kept under observation for over two years of age. The survival rates of all raised offspring generations were not affected by any treatment and the body weights did not show significant differences between control and treated groups. Anymore detailed information on reproductive endpoints is not available from this study since it had been primarily directed to elucidate carcinogenicity.

Developmental toxicity

Only limited information is available on investigations on developmental toxicity. Guideline-conform developmental toxicity studies on methenamine are not available.

During validation of a Screening Assay (Chernoff-Kavlock Assay) modified for studies on rats (Wickramaratne, 1987) methenamine was investigated with a group of 9 female rats treated orally (gavage) during g.d. 7 to 17 with daily doses of 1000 mg/kg bw. In comparison to the concurrent control group a reduced weight gain was observed in treated animals. Compared with the controls, the 5 pregnant dams of the treated group showed no difference in mean litter size, survival of pups and pup postnatal weight gain. However, the number of dams for which offspring could be evaluated is poor, and it is not discussed and no information is given in this study to explain, why only 5 out of 9 sperm-positive dams produced litters.

Effects of methenamine were also investigated in a study with beagle dogs (Hurni and Ohder, 1973). Commercial grade methenamine of unknown source and unknown purity was given at dietary levels of 600 or 1250 ppm (equivalent to doses of 15 or 31 mg/kg bw/day) at days 4 to 56 after mating. From the 11 mated control bitches 9 turned out to be pregnant and provided litters. From the 9 bitches mated in the 15 mg/kg dose group 8 turned out to be pregnant and provided litters. From the 10 bitches mated in the 30 mg/kg dose group 9 turned out to be pregnant. One pregnant bitch in this group was severely injured in a fight and had to be eliminated. Thus only 8 litters were derived from this group. Further groups were treated with two different dosages of formaldehyde (125 and 375 ppm), since the toxicological effects of methenamine were considered to be due to the liberation of formaldehyde (FA). The bitches were weighed at weekly intervals throughout pregnancy and lactation. The pups were weighed at birth and twice weekly thereafter. They were inspected for visible defects immediately after birth and after 8 wk. Stillborn pups and those lost before weaning were autopsied and examined for internal and skeletal abnormalities. Treatment at either dose level did not affect pregnancy rates, mean length of gestation, mean litter size or body weight gain of the mothers. Body weight of the bitches increased regularly during pregnancy in all groups and the duration of gestation was unaffected by the treatment. The mean litter size was within the normal range for all groups (controls, FA 125 ppm, FA 375 ppm, methenamine 600 ppm, methenamine 1250 ppm: 6.7, 5.4, 7.1, 6.3, 7.0). In the group that had received the higher dose of methenamine, the percentage of stillborn pups was higher than in the other groups, due to the fact that in one litter of nine pups only two were born alive. No skeletal or any other malformation were observed in any of the stillborn pups. During the first month there was a

retardation of growth in the group given the higher dose of methenamine, coinciding with an increase in mortality (no data provided). In the same group the percentage of pups that survived to weaning was lower than in the other groups (no data provided). All dogs observed for a more prolonged period have been normal in behavior, appearance, motility and muscular co-ordination. The dogs observed up to 9 months were used for various other investigations, for which they were eventually killed and autopsied. No malformations were found. The 18 dogs transferred to the breeding colony have been under observation for nearly 2 yr. Neither these adults nor their litters have shown any signs of physiological or skeletal abnormalities or disorders of reproduction. The NOAEL/developmental toxicity of this study on dogs is 15 mg/kg bw/d.

Data from investigations on chick embryos (Korhonen et al., 1983a, b) where 0.25 mg methenamine/egg was applied to three-day old embryos in ovo via dropping onto the inner shell membrane did not produce any effects above the background of vehicle controls.

Other information

Several reviews on the toxicology of methenamine (WHO, 1972; Zondlo, 1992) mention further studies, which at the time of evaluation were not (fully) published. The original data were requested but are no longer available; therefore these studies will not be considered for the hazard assessment of methenamine

Human data:

During a clinical study on the pharmacokinetics of methenamine orally applied as methenamine hippurate tablets at a single dose of 1 g to healthy volunteers, methenamine had also been investigated for transplacental transfer in pregnant women during labour and for lactational transfer in nursing mothers (Allgen et al., 1979). Methenamine was found to pass the placental barrier. The concentrations in umbilical cord plasma compared to that in maternal plasma was initially low but reached the levels in maternal plasma after about 4 hours. In amniotic fluid methenamine concentrations were low and varying with no correlation to either the maternal or the umbilical cord plasma levels. When breast milk was analysed five hours after dosing, the methenamine concentrations were of the same magnitude as in maternal plasma. The amount of methenamine uptake by the child during a respective meal was calculated to be far below the usual therapeutic doses (of 5-10 mg/kg body weight) given to adults.

In an Australian clinic, a systematic trial over a 2-year period was made on 206 pregnant women who suffered from asymptomatic bacteriuria (Furness et al., 1974). One special aim was to study the effects of a disease and its special medication with methenamine salts on a number of parameters of pregnancy. The 206 patients were allocated to three treatment groups: (i) 67 patients with no treatment, (ii) 70 patients with 2 g methenamine hippurate/day, (iii) 69 patients with 4 g methenamine mandelate/day. Mean birth weights and gestation lengths showed no significant difference from the control group. The number of abortions, intrauterine deaths and fetal abnormalities in the treated groups did not differ from those of the general population. According to the authors, the statistics of the findings do not support an increase neither in prematurity nor in the incidences of fetal abnormalities or morbidity and a reduction in birth weight.

In a surveillance study conducted between 1985 and 1992 of Michigan Medicaid recipients involving 229101 completed pregnancies, 209 newborns had been exposed to hexamethylentetramine during the first trimester. Eight (3.8%) major birth defects were observed. Nine major birth defects were expected (Briggs et al., 1994).

No congenital abnormalities were observed in the children of 3 women who had taken hexamethylenetetramine as well as 5 other drugs (choleinic sidium, phenolphthalen, papaverine HCL, methylhomatropine, and menthol) during the first two weeks of pregnancy (Siffel & Czeisel, 1995).

Summary and conclusion:

Guideline according studies on methenamine are not available for neither of the two separate endpoints of toxicity to reproduction. Presently available data come from a developmental screening assay and from 3 older single dose mammalian studies in rats and one two dose study with dogs.

During the dietary study with rats (Natvig et al., 1971) the daily dosage of about 100 mg methenamine/kg bw did not reveal any significant effects on the investigated parameters. During the rat study with drinking water administration (Della Porta et al., 1970) the dosage of 1.5-2.5 g /kg bw/day did reveal effects: during the first experiment growth retardation in terms of significantly lower body weights was determined in the pups after weaning. Birth weights and postnatal body weight development of the weanlings had not been determined. Yet, at the beginning of the postweaning weight determinations the initial body weights of the offspring of treated dams was already lower than in the offspring of the controls, indicating that growth deficits were already endowed with. In the second experiment postnatal mortality was observed in the weanlings (F2 generation) of the methenamine exposed groups. Reproductive capacity and capability was not obviously affected during this study. Thus, the dosage of 1.5-2.5 g /kg bw/day may represent a LOAEL for developmental toxicity. During the Chernoff-Kavlock Assay with rats (Wickramaratne, 1987) the dosage of 1 g/kg bw/day (gavage) did not reveal indications for any effects upon pup viability and postnatal pup body weights. However, the number of dams for which offspring could be evaluated is poor, and it is not discussed and no information is given in this study to explain, why only 5 out of 9 sperm-positive dams produced litters. In the study on beagle dogs (Hurni and Ohder, 1973) the daily dosage of 15 mg/kg bw did not produce any significant effects on the development of the offspring, whereas at a daily dosage of 31 mg/kg bw lower pup survival and pup growth retardation were observed.

Taken for its own, neither of these studies sufficiently meets requirements for a sound hazard evaluation with respect to toxicity to reproduction due to poor documentation, use of small animal numbers only, insufficient investigation of reproductive and developmental parameters, and any teratogenic properties not adequately studied. Therefore, the evaluation of the available experimental data can only be based on a synoptic view of all studies.

Taking into consideration that in the rat studies high dose levels (> 1000 mg methenamine/kg body weight/day) had been under investigation, the overall information of these studies may indicate that an overt toxic potential of methenamine adverse to reproductive performance and capability is rather unlikely to be suspected. Methenamine did not reveal a marked potential to adversely affect fertility in rats. Even at longer periods of administration with high doses reproductive capacity and/or capability did not differ from that of the untreated

controls. Thus, the dosage of 1.5-2.5 g/kg bw/day can be considered the NOAEL/fertility from experimental data.

Treatment associated developmentally toxic effects were shown for experimental animals, however, no such effects were observed for the human situation. For both, in rats (at high dosages) as in beagle dogs effects were observed during the postnatal period of development in terms of preweaning mortality and postnatal growth retardation. For the experimental data, from the study of Natvig et al., 1971, the dosage of 100 mg/kg bw/day can be considered the NOAEL/developmental toxicity for rats and from the study of Hurni and Ohder, 1973, the dosage of 15 mg/kg bw/day can be considered the NOAEL/developmental toxicity for dogs. As indicated above, the experimental studies were of limited scope and of questionable validity. Human data on potentially adverse effects to development can be derived from investigations on women that had been treated during pregnancy. In these studies no substance related abnormalities during the course of pregnancy or to the development of the children had been revealed, when mothers had been treated with therapeutic doses of 2 g methenamine hippurate per day (~ 0.9 g methenamine) or 4 g methenamine mandelate per day (~1.9 g methenamine) (corresponding to about 13 to 27 mg methenamine/kg bw/day calculated on an assumed body weight of 70 kg/ person) during the period of pregnancy. Given the limited value of the animal data it is proposed to base quantitaive risk assessment for effects adverse to development on the data resulting from experience in humans (NOAEL 27 mg/kg/day).

4.1.3 Risk characterisation

4.1.3.1 General aspects

Methenamine is rapidly absorbed and excreted (90% of the dose within 12 h) after oral uptake in man. The mean half-life in blood was reported to be 4.3 h. Methenamine can pass the placenta and is detectable in breast milk of lactating women, but no accumulation was seen. There are no kinetic data available from studies following dermal administration or inhalation exposure of methenamine. The systemic availability after oral administration is set at 100% based on animal data, the bioavailability after inhalation is set as 100% by default. The dermal bioavailability is assumed as 50% (default) based on the chemical structure and available physico-chemical data.

Formaldehyde is formed as product of hydrolytic cleavage of methenamine, which is strongly dependent on acidic pH values. Hence, formaldehyde formation is particularly relevant after oral administration (at the acidic pH of the stomach). If formed, formaldehyde can be absorbed into the bloodstream, where it is converted to formic acid very rapidly. The half-life of formic acid is reported to be 55 min. It can be excreted via the kidneys or further oxidised to carbon dioxide and water.

Limited data on the acute toxicity of methenamine in humans are available. Upon skin contact acute dermatitis of the exposed surfaces was the main symptom. In rats, acute toxicity by the oral and dermal routes was proven to be very low with LD50 values of > 20 g/kg bw and 2 g/kg bw, respectively. Data on the inhalation toxicity of methenamine are not available.

Methenamine does not exhibit local irritation by contact with skin or eyes of rabbits. In humans there is some but inconclusive evidence for local skin irritation, which might arise following hydrolysis to formaldehyde and ammonia.

In humans, skin sensitizing properties of methenamine have been described in several reports. Guinea pigs exhibited strong skin sensitization in a maximization test with a 50% aqueous solution of the substance. In addition, methenamine was also positive in a murine Local Lymph Node Assay. In a number of cases allergic symptoms of the respiratory sytem, such as wheezing and asthma, were also reported upon methenamine exposure . However, in all cases exposure to other irritant and sensitizing chemicals occurred simultaneously. The induction of specific respiratory hypersensitivity by methenamine cannot be clearly demonstrated.

There are a number of studies on the health of workers in the steel foundry and in the tire and rubber industry which were repeatedly exposed to methenamine at their workplaces. Deficiencies in the conduct and/or reporting of most of these studies make interpretation of their findings in relation to methenamine difficult. These deficiencies include no or inadequate data on methenamine exposure and/or simultaneous exposures to other chemicals, so that effects could not be clearly attributed to methenamine. In most of the reports the route and extent of exposure was unclear, although a combination of inhalation and dermal exposure was likely.

No complications were observed in patients receiving methenamine orally as a urinary antibacterial-antiseptic at dose levels of 2 to 4 g/d (corresponding to a NOAEL of 57 mg/kg bw/d) for up to four weeks. However, a higher therapeutic dose of 8 g/d (corresponding to about 114 mg/kg bw/d) for 3 - 4 weeks produced bladder irritation, painful and frequent micturition, albuminuria and hematuria.

In several older studies on repeated dose toxicity in experimental animals, no specific organ toxicity was recorded after repeated oral administration (gavage, feeding, or drinking water) up to and including 2.5 g/kg bw/d in rats and in mice. Effects such as albuminuria and hematuria, which were observed in humans, were not confirmed in experimental animal studies. Lifetime exposure to about 61 mg/kg bw/d in the diet to cats did not induce systemic effects. No local and systemic effects in rabbits of both sexes were noted in a subchronic dermal toxicity study using an aqueous methenamine solution at a concentration of 0.20% (equivalent to 1.3 mg/kg bw/d).

Methenamine is weakly positive in bacterial gene mutation assays at extremely high concentrations and in an in vitro chromosomal aberration assay. According to these positive tests the substance seems to have a low mutagenic potential for bacteria and mammalian cells in culture. Negative in vivo chromosomal aberration tests and a negative dominant lethal test indicate that this potential is unlikely to be expressed in germ cells.

Results from retrospective and prospective epidemiology studies on workers in the steel foundry and in the tire and rubber industry did not clearly show a carcinogenic activity of methenamine in humans. The observed increased risks of lung and bladder cancer reported in these studies could not be conclusively attributed to the exposure to methenamine alone as the workers were simultaneously exposed to other chemicals of suspected carcinogenic potency. In addition, mortality studies in this industry area provided no evidence for a causative association between methenamine exposure and cancer in humans. With respect to the use of

methenamine as a drug in humans there is no information available on the formation of tumours in the urinary tract or in other organs or tissues.

There were no animal carcinogenicity studies with methenamine in conformance with the current requirements of carcinogenicity testing by oral, inhalative, or dermal application. However, the carcinogenic potential of methenamine has been investigated in a number of non-guideline long-term/lifetime studies in experimental animals, using the oral route, and involving a variety of strains of rats and mice. From these studies there was no indication of carcinogenic effects in rats and mice following prolonged exposure to high dosages up to and including 2.5 g/kg bw/d methenamine.

A valid cancer study with administration of formaldehyde via drinking water to rats did not demonstrate increased tumor incidences in any organ. Thus it is concluded that the formation of formaldehyde due to the pH dependent cleavage of methenamine in body compartments should be of no concern with respect to carcinogenicity.

High dose levels of methenamine (> 1000 mg/kg bw/d) were investigated in several older studies on reproductive toxicity in rats. The overall information from these studies gives no indication of an overt toxic potential of methenamine adverse to reproductive performance and capability. Methenamine did not reveal a marked potential to adversely affect fertility in rats. Even after extended periods of administration of high doses reproductive capacity and/or capability did not differ from that of the untreated controls. Thus, the dose of 1.5 g/kg bw/d can be considered as the NOAEL/fertility from experimental animal data.

Treatment-associated developmental toxicity was shown in experimental animals, but not in humans. In rats (at high dosages) as well as in beagle dogs effects were observed on postnatal development in terms of preweaning mortality and postnatal growth retardation. As NOAEL/developmental toxicity for rats the dosage of 100 mg/kg bw/d can be derived from the study of Natvig et al. (1971) and for dogs a value of 15 mg/kg bw/d from the study of Hurni and Ohder (1973).

Human data on potential adverse effects on development can be derived from the examination of women who were treated with methenamine salts during pregnancy (Furness et al., 1974). This clinical report gave no indication of a specific impairment of pregnancy outcome or of the development of the children consequent to the therapeutic administration of methenamine in daily doses of 2 g methenamine hippurate or 4 g methenamine mandelate (corresponding to ca.13 and 27 mg methenamine/kg bw/d, respectively). Given the limited value of the animal data it is proposed to base the quantitative risk assessment for developmental effects on the data derived from the experience in humans (NOAEL 27 mg/kg/d).

4.1.3.2 Workers

4.1.3.2.1 Introductory remarks

Methenamine is a solid substance with a vapour pressure of 0.0005 hPa at 20°C, a molecular weight of 140.2 g/mol, a calculated partition coefficient (log P_{OW}) of –4.15 and a high solubility in water (667 g/l). Methenamine is a weak base in aqueous solution (pH 8.4 of a

0.2 M solution). The substance is added as a hardening component during the production of powdery or liquid preparations of phenolic resins and phenolic resins moulding compounds. In addition, the preparations are used as binders in formed or unformed fireproof materials.

The occupational exposure scenarios have been described and discussed in detail in section 4.1.1.2. The exposure routes to be considered in connection with the workplace are exposure by inhalation or dermal contact. Due to the physico-chemical properties of the substance inhalative and dermal exposure to dusts during the handling of the powdery substance or powdery preparations is expected to be the main source of exposure. Additionally especially dermal contact may occur during cleaning, repair and decoupling of transfer lines. The exposure values as reported in tables 4.2 and 4.3 are carried forward for inhalative and dermal risk assessment.

The toxicological data on methenamine are described and discussed in section 4.1.2. Approximately 10-20 % of orally applicated methenamine is converted to formaldehyde and ammonia in the acidic ambiance of the stomach (Gleckman et al., 1979). This pH-dependent reaction decreases at increasing pH-values. Because of the more neutral area of the respiratory tract and the skin the formation of formaldehyde after inhalation or dermal contact is considered to be low and will not be further discussed in detail in this risk assessment. Relevant human toxicity data are available, because methenamine is used for the prevention of recurrent urinary infections in man. These human data are especially used to assess repeated dose and reproductive toxicity. For other toxicological endpoints risk estimations are mainly based on experimental animal data. The threshold levels identified in the hazard assessment part of the report are taken forward to occupational risk assessment. Repeated dose toxicity, developmental toxicity, and sensitisation might be addressed as the most significant effects in the toxicological profile of methenamine.

Systemic availability for different routes of exposure

For the majority of toxicological endpoints methenamine data originate from oral studies. Since workers are exposed either by inhalation or by skin contact, route-to-route transformation is essential for the occupational risk assessment. It is recognized, that route-to-route extrapolation is associated with a high degree of uncertainty.

Concerning the oral route a rapid absorption of methenamine and its salts from the intestinal tract is described. A smaller part of methenamine is yet cleaved in the acid atmosphere of the stomach, but overall a 100% systemic availability of methenamine or its metabolites after oral intake can be assumed. There are no data known concerning absorption after inhalation or dermal application (see chapter 4.1.2.1). For methenamine, acute oral and dermal studies are available, but these toxicity studies can not be used to conclude on route-specific absorption for other toxicological endpoints. With reference to the chapter on toxicokinetics a 100% absorption by inhalation and a 50% dermal absorption is taken forward to risk characterisation. No measurement data about the particle size distribution of the inhalative fraction of methenamine are available.

Occupational exposure and internal body burden

In table 4.6 the exposure levels of tables 4.2 and 4.3 are summarised and the route specific and total internal body burden is identified.

Table 4.6: Methenamine exposure levels which are relevant for occupational risk assessment and internal body burden

Exposure scenario			Inhalation shift average (mg/m^3)	Dermal contact shift average (mg/p/d)	Internal body burden of workers after repeated exposure (mg/p/d)		
					Inhalation[(1)]	Dermal[(2)]	Combined
1a	Production and further processing to explosives (with LEV)	dusty material	4[(3)]	4.2[(6)]	40	~2	42
1b		low dust material	0.2[(3)]	4.2[(6)]	2		4
2.	Formulation of phenolic resin systems		12[(5)]	3000[(5)]	120	1500	1620
3.	Production of fuel tablets (97% methenamine)		5[(4)]	420[(4)]	50	210	260
4.	Production of formulations used in corrosion prevention and as photochemicals		1[(5)]	420[(4)]	10	210	220
5.	Use of phenolic resin systems (up to 15 % methenamine)		7.5[(4)]	126[(4)]	75	63	138

[(1)] based on the assumption of 100% inhalative absorption; breathing volume of 10 m^3 per shift
[(2)]based on the assumption of 50% systemic availability of methenamine after dermal contact
[(3)]measurement data
[(4)]EASE-estimation
[(5)]analogous data
[(6)]EASE-estimation with 90% protection by suitable gloves

Calculation of MOS values

MOS values are calculated as quotient of experimental NOAEL (or LOAEL) from animal or human studies and workplace exposure levels. If the route of application in animal or human studies is different from the actual occupational exposure, the dose units of the experimental and the exposure data have to be adapted previously to MOS calculation. As result of this adaptation a “starting point” for the MOS calculation is identified.

The exposure routes considered in occupational risk assessment are inhalation and dermal contact. The MOS values for exposure by each route are considered separately. The combined MOS-value is calculated as quotient of the internal NAEL (i. e. the external NOAEL multiplied with the percentage of absorption) and the internal body burden.

With respect to the possible outcome of an assessment for combined risks, interest focuses on scenarios with conclusion ii at both exposure routes. Based on theoretical considerations, combined exposure will not increase the most critical route-specific risk component more than twice. Against this background it is recognized that combined risks only rarely determine concern.

Evaluation of MOS values

Risk assessment based on MOS values implies the identification of a minimal MOS as decision mark between conclusion ii and iii. In order to get consistent conclusions for different chemicals, substance-specific adjustment factors, which may vary depending on data availability and the specific toxicological endpoint to be evaluated, are identified. Scientifically based adjustment factors describe the extrapolation of animal data to the worker population. The uncertainties in the specific calculations are weighed by expert judgement and are expressed as an additional "uncertainty factor". The value of the minimal MOS results from the multiplicative combination of these different assessment factors.

If the MOS value for a certain exposure scenario is below the minimal MOS, the corresponding risk situation is considered to be of concern. A MOS value higher than the minimal MOS indicates no concern.

In a parallel procedure, which gives identical but more direct results, the toxicological starting point taken forward to risk characterisation may be divided by the endpoint-specific assessment factors. As a result, an exposure level is identified for methenamine which by direct comparison with the occupational exposure levels may serve as trigger for decisions. In the context of this risk assessment report it will be called "critical exposure level". Concern will be expressed for scenarios above this trigger value.

Interspecies differences

Because of relevant human data, interspecies extrapolation for methenamine is not necessary for repeated dose toxicity and for developmental toxicity.

For other endpoints species differences might exist concerning the susceptibility for methenamine toxicity. However no information on the relative sensitivity of humans is available. There is no mechanistic argument to suggest that findings are restricted to animals and should not be transferred to humans. For the purpose of occupational risk assessment, scaling on the basis of metabolic rate is used as a default assumption for interspecies extrapolation.

For interspecies extrapolation of oral or dermal data metabolic rate scaling results in lower effective dose levels in mg per kg bodyweight for humans compared to experimental animals. For mice the scaling factor is 7, for rats 4 and for rabbits 2.2 (NO-NL, 1999). The scaling factor is calculated by the formula $(BW_{human}/BW_{animal})^{0.25}$.

For inhalation the principle of metabolic rate scaling implies that a specific inhalation exposure level (in mg/m^3) is toxicologically equivalent in experimental animals and humans. However, care has to be taken to rely the extrapolation between species on directly comparable conditions: under study conditions rats are thought to be at a state of reduced activity; the according human breathing volume in 8 hours is 6.7 m^3(0.2 l/min/kg x 60 min/h x 70 kg). Workers are assumed to breathe 10 m^3 during a normal working day under conditions of light to moderate activity. Thus for workers the amount of substance inhaled must be spread over a 1.5 times higher breathing volume. Maintaining toxicological equivalence

means that, compared to the experimental levels, the corresponding occupational air conditions will be 1.5 times lower.

Duration adjustment

For chemical substances it is usually expected that the specified effect concentrations decrease with increasing duration of application. Available experimental data for methenamine are difficult to interpret in terms of duration dependency of adverse effects. If necessary, considerations on duration adjustment are outlined in the endpoint-specific risk assessment. Where adaptation of daily or weekly doses is necessary, e.g. in the calculation of totally administered amounts of methenamine, a linear adjustment is used.

Intraspecies differences

Humans differ in sensitivity due to biological factors. The actual risks for a single person may either be less or more pronounced than estimated for the average human. It is recognised that in order to cover the most sensitive person a very high default assessment factor would be required.

Based on an evaluation of empirical data by Schneider et al. (2004) it is anticipated that a factor of 5 will be sufficient to protect the major part of the worker population (about 95%). Using a lower factor of 3, for instance, about 90% of the population would be protected whereas a factor of 10 would include 99% of the population. The empirical data do not allow to decide, if a lower factor would be sufficient for certain toxicological effects, like for instance local effects in the airways. In the absence of further specific information a default intraspecies variation factor for local effects is not defined.

For risk assessment of repeated dose toxicity and developmental toxicity of methenamine human data are used. Thus the described NOAEL is based on human evidence. So the assumption is made, that the exposed group of persons does contain individuals who are more sensitive than the average of the individuals. To account for this aspect a factor lower than 5 is used. An intraspecies factor of 3 is applied in the assessment of these specific endpoints.

Uncertainty considerations

The adjustment factors outlined above serve to adapt animal data to humans. They rely mainly upon evaluation of literature data for different chemicals. From a statistical point of view the individual parameters have to be understood as point estimates belonging to probability density functions. Each factor is taken as geometric mean (point near the maximum of its distribution) from its density function. The multiplicative combination of all factors is therefore supposed to result in a central tendency estimate. It addresses a likely situation for that percentile of the population reflected by the intraspecies factor.

To complete the assessment, the uncertainty included in the procedure outlined above should be addressed and, if necessary, be used to modify the minimal MOS in terms of precaution. On that purpose several aspects should be taken into account, which by their nature are not easy to quantify. Examples are the reliability of the data base, the biological relevance of the observed effects, the variablity in assessment factors or the different steps necessary to bridge data gaps.

4.1.3.2.2 Occupational risk assessment

Acute toxicity

Systemic effects (inhalation)

Human or animal data with inhalation exposure are not available. Oral rat studies led to no lethality up to the highest tested dose of >20 g/kg. The starting point for human dose calculates to 140,000 mg/m^3 (20,000 mg/kg x 70 kg / 10 m^3). The highest inhalative exposure level of 12 mg/m^3 results from scenario 2 (formulation of phenolic resin systems). The according MOS value of 11,700 (starting point 140,000 mg/m^3 / exposure of 12 mg/m^3) is considered to be high enough to exclude acute toxic effects at these exposure conditions. This general evaluation for acute inhalation toxicity is convincingly supported by the MOS approach for repeated dose toxicity which does not result in any corresponding concern.

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

Systemic effects after dermal contact

For rats, acute toxicity has proven to be very low. In a dermal rat study under occlusive conditions no lethality or other alterations after necropsy were detected at a dose of 2000 mg/kg. Because of that rather low acute toxicity without indication for acute effects at the highest dermal dose tested health risks by acute dermal contact are not anticipated to occur.

This general evaluation for acute dermal toxicity might be backed by the human data on repeated oral toxicity. 8000 mg/person/day for some weeks produced side effects in humans. The single dose for these side effects might even be higher. Assuming a 50% dermal absorption rate the corresponding external dermal dose with side effects following repeated exposure is 16.000 mg/person/day. Against that background, without further adjustment of this dose for acute effects and possible intraspecies differences, relevant acute dermal risks are not anticipated to occur even in scenario 2 with a very high dermal exposure of presumably 3000 mg/person/day. Because of the low acute toxicity of methenamine, health risks after combined expoure are also not anticipated to occur.

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

Irritation/Corrosivity

Skin

Methenamine is not a local irritant by contact with skin and eyes of rabbits. In contrast to animal data, dermal exposure of methenamine in humans may cause local skin irritancy.

Conclusion ii is proposed on the grounds that control measures exist (methenamine is a skin sensitising substance) which can minimise dermal exposure and risk of irritation, thereby reducing concern. However, these controls must be implemented and complied with to reduce the risk of damage to skin.

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

Eyes

Human data are not available. In rabbits methenamine is not irritating under the conditions of guideline tests. Thus methenamine is not considered to be an eye irritant under acute exposure conditions.

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

Inhalative irritation

There are data on respiratory irritation in humans caused by fumes containing methenamine and its decomposition products ammonia and formaldehyde that mainly reflect the well known irritative property of the decomposition products. For methenamine itself, experimental data on respiratory tract irritation are not available. Against the background of a low skin and eye irritation potential conclusion ii for inhalative irritation seems to be justified.

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

Sensitisation

Skin

Whilst methenamine has not clearly demonstrated skin sensitizing properties in humans, guinea pigs exhibited strong skin sensitization in a maximization test with a 50% aqueous substance solution (R 43 "May cause sensitization by skin contact").

In all dermal scenarios the formulations with methenamine are considered to be skin sensitising (concentration of methenamine greater than 1%). Therefore concern is expressed for all dermal occupational exposure scenarios. For skin sensitisation, there are no data to give a quantitative description of risk. For scenario 1, for which a relevant exposure reduction by suitable gloves is assumed, the risk of skin sensitisation is considered significantly lower than for the other scenarios.

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

Respiratory Sensitisation

Animal data on respiratory sensitisation are not available. In a number of human cases allergic symptoms such as wheezing and asthma were reported upon exposure to methenamine. In all cases exposure to other irritant and sensitising chemicals occurred simultaneously. The respiratory hypersensitivity could not specifically be related to methenamine exposure. From a well-documented recent study that was designed to analyse the sensitising potential of methenamine, there was no evidence that methenamine alone may cause respiratory sensitisation after occupational exposure (Merget et al., 1999).

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

Repeated dose toxicity

Inhalation (local effects)

Animal studies with acute or repeated inhalation exposure are not available. There are data (case reports from workers in foundries, rubber, and resin industry) on respiratory irritation in humans caused by fumes containing methenamine and its decomposition products ammonia and formaldehyde that mainly reflect the well known irritative property of the decomposition products. There is no indication that current exposure levels of methenamine itself may cause serious chronic effects at the site of initial contact.

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

Dermal contact (local effects)

Limited information results from a subcronic dermal study in rabbits (5 days a week for a period of 6 weeks). After dermal non-occlusive application of 0.2% methenamine no signs of local or systemic effects at the skin of rabbits were observed (Zondlo, 1992). Besides this information of animal experiments with the relative low methenamine concentration no data on repeated dermal exposure are available.

Due to the fact that methenamine has skin sensitising properties, a relevant reduction in dermal exposure is necessary and special concern for repeated dermal contact is not expressed.

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

Systemic effects (RDT) by inhalation, dermal contact and combined exposure

Relevant human or experimental data on dermal or inhalation toxicity are not available. Therefore, oral data are taken into account for the assessment of systemic effects after repeated inhalation and dermal contact.

A number of repeated dose toxicity studies by oral administration in animals showed, that methenamine did not cause any toxic effects up to and including 2500 mg/kg/day.

From the use of methenamine for the prevention of recurrent urinary infections in man it is known that dose levels of 2000 to 4000 mg/day (equivalent to about 28 to 57 mg/kg bw/day calculated on a calculated body weight of a 70 kg person) produced no harmful reactions or complications. Therapeutic doses of 8000 g/day (equivalent to 114 mg/kg/day) for 3 to 4 weeks produced side effects such as bladder irritation, painful and frequent micturition, albuminuria and hematuria. The human NOAEL of 57 mg/kg/day is identified as the most sensitive one (see chapter 4.1.2.6) and will be used for risk characterisation.

Because of 100% oral absorption, the internal starting point is 4000 mg/person/day (57 mg/kg/day x 70). Because of the assumption of 100% absorption by inhalation the external starting point for inhalation is 400 mg/m^3 (4000 mg/person/day / 10 m^3/day). For dermal absorption a percentage of 50% is taken forward. This results in an external starting point for dermal contact of 8000 mg/person/day.

The following assessment factors are applied for the identification of the minimal MOS:

- adaptation of scenarios (therapeutic use 7 days/week to 5 days/week for workers) reveals a factor of 5/7
- for duration adjustment (“subacute” to chronic) a factor of 6 is used
- to account for intraspecies differences a factor of 3 will be used (see chapter 4.1.3.2.1)

The multiplication of these factors produces a minimal MOS of ~13 (5/7 x 6 x 3). The corresponding critical exposure levels are calculated as 31 mg/m^3 for inhalation (400 mg/m^3 / 13) and 620 mg/person/day for dermal contact (8000 mg/person/day / 13). The internal critical exposure level for combined exposure is 310 mg/person/day (4000 mg/person/day / 13).

Table 4.7: MOS values for repeated dose toxicity of methenamine, systemic effects

			Inhalation			Dermal			Combined		
Starting point for MOS calculation			400 mg/m^3			8000 mg/p/d			4000 mg/p/d		
Minimal MOS			13			13			13		
Critical exposure level			31 mg/m^3			620 mg/p/d			310 mg/p/d		
			Exposure (mg/m^3)	MOS	Conclusion	Exposure (mg/p/d)	MOS	Conclusion	Exposure (mg/p/d)	MOS	Conclusion
1a	Production and further processing to explosives (with LEV)	dusty material	4	100	ii	4.2	1900	ii	42	95	ii
1b		low dust material	0.2	2000	ii				4	1000	
2.	Formulation of phenolic resin systems		12	33	ii	3000	2,7	iii	1620	2,5	iii[(1)]
3.	Production of fuel tablets (97% methenamine)		5	80	ii	420	19	ii	260	15	ii
4.	Production of formulations used in corrosion prevention and as photo chemicals		1	400	ii	420	19	ii	220	18	ii
5.	Use of phenolic resin systems (up to 15% methenamine)		7.5	53	ii	126	63	ii	138	29	ii

[(1)]Conclusion iii already results from dermal exposure, therefore it does not seem specific for combined exposure scenarios

Based on this MOS approach, there is no concern for exposure by inhalation. Dermal exposure proves to be more critical: For this route of exposure, conclusion iii is reached for scenario 2 (formulation of phenolic resin systems). While scenario 2 is assessed as a clear-cut concern-scenario, scenario 3 (production of fuel tablets) and scenario 4 (production of formulations used in corrosion prevention and as photo chemicals) are considered to be borderline situations, for which no concern is expressed.

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

Mutagenicity

Methenamine seems to have a low mutagenic potential in vitro. The negative in vivo chromosomal aberration test and the negative dominant lethal test indicate that this potential is unlikely to be expressed in vivo.

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

Carcinogenicity

Human data provide no evidence for a causative association between methenamine exposure and cancer in humans. In long-term animal studies in rats and mice no indication of a carcinogenic property was detected. With specific reference to the hazard assessment part of this report it is concluded that formaldehyde (due to the pH dependent cleavage of methenamine in body compartments) should be of no concern for workers with respect to 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

Reproductive toxicity

Fertility impairment

The database for the assessment of toxicity for reproduction from animal studies is poor and the available data are of limited value. Dose-response studies have not been performed. High dose levels (1.5 g/kg bw/d) did not reveal fertility impairment in rats (Della Porta et al., 1970). Because there is no indication for adverse fertility effects, a MOS approach is not performed.

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

Developmental toxicity

Treatment associated developmental effects were shown for experimental animals. In beagle dogs effects were observed during the postnatal period of development in terms of preweaning mortality and postnatal growth retardation. As NOAEL/developmental toxicity for dogs a value of 15 mg/kg bw/d from the study of Hurni and Ohder (1973) can be derived. This study does not sufficiently meet the requirements for a sound hazard evaluation and risk characterisation with respect to toxicity to reproduction due to poor documentation, use of

small animal numbers only, and insufficient investigation of reproductive and developmental parameters.

Human data on potentially adverse effects to development can be derived from investigations on women that had been treated with methenamine salts during pregnancy (Furness et al., 1974). In this systematic trial women had been treated with therapeutic doses of 2 g methenamine hippurate per day or 4 g methenamine mandelate per day (corresponding to about 13 or 27 mg methenamine/kg bw/d) during the period of pregnancy. No substance related abnormalities during pregnancy or development of the children had been revealed.

Although there were no effects in treated pregnant women observed, a MOS calculation will be done, because the dog data (see above and chapter 4.1.2.9) cannot be completely discounted. The calculation is based on the data resulting from experience in pregnant women and starts with the NOAEL of 27 mg/kg bw/d. This corresponds to a starting point of 1890 mg/person/day (27 mg/kg/day x 70 kg). Including the aspect of 50% dermal absorption the corresponding dermal dose (external value) is calculated as 3780 mg/person/day (1890 mg/person/day x 2). Expressed as air-borne concentration the starting point is 189 mg/m^3 (1890 mg/person/day / 10 m^3).

For risk assessment of developmental toxicity (and repeated dose toxicity) of methenamine human data are used. Thus the described NOAEL is based on human evidence. So the assumption is made, that the exposed group of persons does contain individuals who are more sensitive than the average of the individuals. To account for this aspect a factor lower than 5 is used. An intraspecies factor of 3 is applied in the assessment of these specific endpoints.The following factors are applied for the identification of the minimal MOS:

The following factors are applied for the identification of the minimal MOS:

- to account for intraspecies differences a factor of 3 will be used (see chapter 4.1.3.2.1)

- a factor of 3 is used to consider the severity of possible developmental effects.

Altogether the minimal MOS calculates to 9 (3 x 3). The corrresponding critical exposure levels are calculated as 21 mg/m^3 for inhalation (189 mg/m^3 / 9), 420 mg/person/day as external dose for skin contact (3780 mg/person/day / 9) and 210 mg/person/day as internal dose for evaluation of combined exposure (1890 mg/person/day / 9).

Table 4.8: MOS values for developmental toxicity of methenamine

			Inhalation			Dermal			Combined		
Starting point for MOS calculation			189 mg/m^3			3780 mg/p/d			1890 mg/p/d		
Minimal MOS			9			9			9		
Critical exposure level			21 mg/m^3			420 mg/p/d			210 mg/p/d		
			Exposure (mg/m^3)	MOS	Conclusion	Exposure (mg/p/d)	MOS	Conclusion	Exposure (mg/p/d)	MOS	Conclusion
1a	Production and further processing to explosives (with LEV)	dusty material	4	47	ii	4.2	900	ii	42	45	ii
1b		low dust material	0.2	950	ii				4	470	
2.	Formulation of phenolic resin systems		12	16	ii	3000	1.3	iii	1620	1.2	iii[(1)]
3.	Production of fuel tablets (97% methenamine)		5	38	ii	420	9	iii	260	7.2	iii[(1)]
4.	Production of formulations used in corrosion prevention and as photo chemicals		1	189	ii	420	9	iii	220	8.6	iii[(1)]
5.	Use of phenolic resin systems (up to 15% methenamine)		7.5	25	ii	126	30	ii	138	13.7	ii

[(1)]Conclusion iii already results from dermal exposure, therefore it does not seem specific for combined exposure scenarios

Based on this MOS approach, there is no concern for exposure by inhalation. Dermal exposure proves to be more critical: For this route of exposure, conclusion iii is reached for scenario 2 (formulation of phenolic resin systems), 3 (production of fuel tablets) and 4 (production of formulations used in corrosion prevention and as photo chemicals). While scenario 2 is assessed as a clear-cut concern-scenario, scenario 3 and 4 is considered to be a borderline situation.

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

4.1.3.2.3 Summary of conclusions for the occupational risk assessment

Table 4.9 formally indicates the toxicological endpoints of concern for methenamine. There is concern for skin sensitisation, repeated dose toxicity, and developmental toxicity.

Table 4.9: Endpoint-specific overall conclusions for methenamine

Toxicological endpoints		general conclusion
Acute toxicity	inhalation	ii
	dermal	ii
	combined	ii
Irritation/ Corrosivity	dermal	ii
	eye	ii
	acute respiratory tract	ii
Sensitisation	skin	iii
	respiratory	ii
Repeated dose toxicity	local, inhalation	ii
	local, dermal	ii
	systemic, inhalation	ii
	systemic, dermal	iii
	systemic, combined	iii (1)
Mutagenicity		ii
Carcinogenicity	inhalation	ii
	dermal	ii
	combined	ii
Fertility impairment	inhalation	ii
	dermal	ii
	combined	ii
Developmental toxicity	inhalation	ii
	dermal	iii
	combined	iii(1)

(1) conclusion iii already results from dermal exposure, therefore it does not seem specific for combined exposure scenarios

In table 4.10 occupational exposure scenarios are listed to give an overview for all exposure situations with concern. Only those toxicological endpoints are listed, which give reason for conclusion iii. For methenamine concern results from dermal contact to the substance (skin sensitisation, developmental toxicity and systemic effects after repeated dermal contact).

Table 4.10: Exposure scenarios with concern for methenamine

Exposure scenario		Sensitisation		Developmental toxicity			Repeated dose toxicity, systemic		
		inhalation	skin	inhalation	dermal	combined	inhalation	dermal	combined
1.	Production and further processing to explosives	ii	iii	ii	ii	ii	ii	ii	ii
2.	Formulation of phenolic resin systems	ii	iii	ii	iii	iii	ii	iii	iii
3.	Production of fuel tablets (97% methenamine)	ii	iii	ii	iii	iii	ii	ii	ii
4.	Production of formulations used in corrosion prevention and as photochemicals	ii	iii	ii	iii	iii	ii	ii	ii
5.	Use of phenolic resin systems (up to 15% metheneamine	ii	iii	ii	ii	ii	ii	ii	ii

In table 4.11 the dermal exposure scenarios are ranked by the level of dermal exposure.

For skin sensitisation, there are no data to give a quantitative description of risk. For scenario 1, for which a relevant exposure reduction by suitable gloves is assumed, the risk of skin sensitisation is considered significantly lower than in the other scenarios.

For developmental toxicity, scenario 3 (production of fuel tablets) and 4 (production of formulations used in corrosion prevention and as photo chemicals) reach borderline. For the borderline situation concern is expressed. Scenario 2 is considered to be a clear-cut concern situation, also for the endpoint repeated dose toxicity. Special emphasis has to be given to significantly reduce dermal contact during formulation of phenolic resin systems (scenario 2).

Table 4.11: Ranking of dermal exposure scenarios

Exposure scenario	Exposure level in mg/person /day	Sensitisation	Developmental toxicity	Systemic repeated dose toxicity .
		Critical exposure level in mg/person/day		
			420	620
2. Formulation of phenolic resin systems	3000	iii	iii	iii
3. Production of fuel tablets (97% methenamine)	420	iii	iii	ii
4. Production of formulations used in corrosion prevention and as photo chemicals	420	iii	iii	ii
5. Use of phenolic resin systems (up to 15% methenamine	126	iii	ii	ii
1. Production and further processing to explosives	4.2	iii	ii	ii

4.1.3.3 Consumers

Consumer Exposure

Methenamine is used as a component of cosmetics resulting in an external dermal exposure of 0.45 mg/kg bw/d corresponding to an internal exposure of 0.225 mg/kg bw/d. A local skin contact of some consumers may also occur from use of solid fuel tablets containing methenamine. Oral exposure may result from the intake of provolone cheese (0.021 mg/kg bw/d). The main route of potential consumer exposure is assumed to be via dermal contact.

Acute Toxicity

Human data on acute toxicity are not available. From limit tests with rats, a dermal LD50 value for methenamine could not be derived as the highest tested dose of 2000 mg/kg bw resulted in no clinical signs or symptoms of toxicity in the test animals. The acute toxicity of methenamine in rats after oral adminisatration was also proven to be very low (LD50 >20 g/kg bw). According to the exposure assessment, consumers are exposed to methenamine in concentrations several orders of magnitude lower than those tested in toxicity tests. Therefore, the substance is of no concern for the consumer in relation to acute dermal or oral 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

Irritation

Methenamine is not a local irritant by contact with skin and eyes of rabbits. Available evidence for local skin irritation in humans is inconclusive. Conclusion (ii) is proposed on the grounds that the available data base does not warrant a classification of methenamine as “irritant” and that risk reduction measures to be proposed on account of its skin sensitizing properties will also protect against skin irritation.

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

Corrosivity

Methenamine did not show local corrosivity.

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

Sensitization

In humans, methenamine has demonstrated some skin sensitizing properties. Guinea pigs exhibited strong skin sensitization. In addition, methenamine was also positive in a murine Local Lymph Node Assay.

According to the exposure assessment, dermal exposure of consumers to methenamine is primarily expected from low levels of the substance contained in cosmetics (max. allowed level as preservative 0.15%). However, higher concentrations in cosmetics are permitted for other specific purposes. Besides, even at low concentrations it cannot be excluded that skin sensitization will occur.

Brief local skin contact may also occur from application (handling/breaking) of solid fuel tablets containing methenamine in a high percentage (97%). A possible concern with respect to skin sensitization due to this use cannot be totally excluded.

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

Repeated dose toxicity

No complications were observed in patients receiving methenamine as an urinary antibacterial-antiseptic at dose levels of 2 - 4 g/d (corresponding to ca. 28 t- 57 mg/kg bw/d based on a body weight of 70 kg) for up to 4 weeks. Higher doses of 8 g/d (corresponding to 114 mg/kg bw/d) for 3 - 4 weeks induced urological abnormalities such as bladder irritation, painful and frequent micturition, albuminuria, and hematuria.

In experimental animals no methenamine-induced lesions were observed after long-term exposure up to and including 2.5 g/kg bw/d in rats and mice. Lifetime exposure of cats to 60.65 mg/kg bw/d methenamine in the diet did not induce relevant toxic effects. Repeated dermal application of an aqueous methenamine solution to rabbits in a concentration of 0.20% (equivalent to 1.3 mg/kg bw/d) did not cause local or systemic effects in both sexes.

For the decision on the appropriateness of MOS, the following aspects have been considered and taken into account:

- overall confidence in the database

The data taken into account for performing the risk characterisation have been evaluated with regard to their reliability, relevance and completeness according to section 3.2 of the TGD. There is no study available which is performed in accordance with internationally recognized guidelines and GLP standards. However, the overall information derived from all studies is not contradictory so that a judgement can be based on this database.

- uncertainty arising from the variability in the experimental data

The studies cited above allow to conclude on the NOAEL for repeated application of the substance. The NOAEL of 57 mg/kg bw/d derived from data on the therapeutic use of the

substance in humans by the oral route is considered to be the most appropriate value for risk assessment.

Limited information available from a subchronic dermal study in rabbits (NOAEL of 1.3 mg/kg/d) is not considered to provide an appropriate database for risk assessment, since the only tested dose is very low, an effective dose was not determined, and the description of the study is very poor.

There are no reasons to assume a special extent of uncertainty which has to be taken into account.

- intra- and interspecies variation

Data on kinetics of the substance do not allow to calculate the intraspecies and interspecies variability by applying modern approaches. However, since the risk assessment can be based on human data (Goodman and Gilman data on patients), considerations on interspecies variations are not necessary.

- the nature and severity of the effect

The effects observed at higher therapeutic doses in humans are considered to be severe health effects. Animal studies with oral administration showed that methenamine did not cause any toxic effects up to doses of 2.5 g/kg bw/d.

- differences in exposure (route, duration, frequency and pattern)

The estimated dermal and oral exposures (with assumed absorption percentage of 50% and 100%, respectively) are compared with an oral NOAEL derived from data on the therapeutic use of the substance in humans.

- the human population to which the quantitative and/or qualitative information on exposure applies

Following the exposure pattern there is no reason to assume a special risk for children, elderly, or pregnant women.

- other factors

There are no other factors known requiring a particular margin of safety.

MOS for the dermal exposure scenario:

The maximum daily external exposure to cosmetics has been calculated to be 0.45 mg/kg bw/d corresponding to an internal exposure of 0.225 mg/kg bw/d. The margin of safety between the

internal exposure level of 0.225 mg/kg bw/d

and the

NOAEL (human) of 57 mg/kg bw/d

is judged to be sufficient.

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

MOS for the oral exposure scenario:

An oral exposure of 0.021 mg/kg bw/d has been calculated from an assumed daily intake of 50 g provolone cheese. The margin of safety between the

exposure level of 0.021 mg/kg bw/d

and the

NOAEL (human) of 57 mg/kg bw/d

is judged to be sufficient.

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

Mutagenicity

Methenamine is weakly positive in extremely high concentrations in bacterial gene mutation assays and in a chromosomal aberration assay. According to these positive tests the substance seems to have a low mutagenic potency towards bacteria and mammalian cells in culture. Negative in vivo chromosomal aberration tests and a negative dominant lethal test indicate that this potential is unlikely to be expressed in germ cells.

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

Carcinogenicity

Several cohort and mortality studies are available covering workers in the steel foundry and in tire and rubber plants, which were exposed to methenamine contained in mixtures with several other chemicals. In these studies, there was no clear evidence for a causal relationship between specific cancer mortality and exposure to methenamine. Nevertheless, among the workers an excess incidence of lung and bladder tumours was noted. However, detailed analyses of these data, together with the aspect that workers were simultaneously exposed to other chemicals at their workplaces, suggest that methenamine alone cannot be evaluated as a likely causative agent. Furthermore, the available mortality studies in this industry area

provide no evidence for a causal association between methenamine exposure and cancer in humans.

With respect to the use of methenamine as a drug in humans there is no information available on the formation of tumours in the urinary tract nor in other organs or tissues.

A number of long-term oral (gavage, feeding, drinking water) studies in experimental animals, using a variety of strains of rats and mice are available, some involving high dose levels up to and including 2.5 g/kg bw/d. None of these studies fully meets modern protocols for carcinogenicity studies. From these studies there was no firm indication on carcinogenic effects in rats or mice. In the light of negative in vivo mutagenicity tests, concern is not to be expected.

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

Toxicity for reproduction

Fertility impairment

High dose levels of methenamine (> 1000 mg/kg bw/d) were investigated in several older studies on reproductive toxicity in rats (Della Porta et al., 1970). The overall information from these studies gives no indication of an overt toxic potential of methenamine adverse to reproductive performance or capability. Methenamine did not reveal a marked potential to adversely affect fertility in rats. Even after extended periods of administration of high doses reproductive capacity and/or capability did not differ from that of the untreated controls. Thus, the dose of 1.5 g/kg bw/d is considered as the NOEL/fertility from experimental animal data.

MOS for the dermal exposure scenario

The daily external exposure of consumers to cosmetics has been calculated to be 0.45 mg/kg bw/d corresponding to an internal exposure of 0.225 mg/kg bw/d. The margin of safety between the

internal exposure level of 0.225 mg/kg bw/d

and the

NOEL of 1500 mg/kg bw/d

is judged to be sufficient.

MOS for the oral exposure scenario

An oral exposure of 0.021 mg/kg bw/d has been calculated from an assumed daily intake of 50 g provolone cheese. The margin of safety between the

exposure level of 0.021 mg/kg bw/d

and the

NOEL of 1500 mg/kg bw/d

is judged to be sufficient.

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

Developmental toxicity

Treatment-associated developmental toxicity was observed in experimental animals, but not in humans. In rats (at high dosages) as well as in beagle dogs effects were observed on postnatal development in terms of preweaning mortality and postnatal growth retardation. As NOAEL/developmental toxicity for rats the dosage of 100 mg/kg bw/d can be derived from the study of Natvig et al. (1971) and for dogs a value of 15 mg/kg bw/d from the study of Hurni and Ohder (1973).

Human data on potential adverse effects on development can be derived from the examination of women who were orally treated with methenamine salts during pregnancy (Furness et al., 1974). These investiagtions revealed no substance related abnormalities with regard to the course of pregnancy or the development of the children consequent to the therapeutic administration of 2 g methenamine hippurate per day or 4 g methenamine mandelate per day (corresponding to ca. 13 and 27 mg methenamine/kg bw/d, respectively)

Given the limited value of the animal data the risk assessment for adverse effects on development is based on the data derived from experience in humans (NOAEL 27 mg/kg bw/d).

For the decision on the appropriateness of MOS, the following aspects regarding the critical effect as well as exposure have been considered and taken into account:

- overall confidence in the database

The data taken into account for performing the risk characterization have been evaluated with regard to their reliability, relevance and completeness according to section 3.2 of the TGD. There is no study available which is performed in accordance with internationally recognized guidelines and with GLP standards. However, since the overall findings derived from all studies are not contradictory, a judgement can be based on this database (cf. 4.1.2.9).

There are no reasons to assume limited confidence.

- uncertainty arising from the variability in the experimental data

No special concerns have to be raised from this point. The NOAEL of 27 mg/kg bw/d, derived from the therapeutic use of the substance in women, is considered to be the most appropriate value for risk assessment.

- intra- and interspecies variation

Data on the kinetics of the substance do not allow to calculate the intraspecies and interspecies variability by applying modern approaches. In using the Furness et al. (1974) data derived from human experience considerations on interspecies variations are not necessary. There is indication that dogs are more susceptible to methenamine than rats.

- the nature and severity of the effect

The effects in dogs and rats (at high dosages) are considered to be severe health effects. However, human data are available from investigations on women that had been treated with methenamine salts during pregnancy. No substance related abnormalities during the course of pregnancy or to the development of the children had been revealed on treatment with therapeutic doses of 2 g methenamine hippurate per day or 4 g methenamine mandelate per day during the period of pregnancy.

- dose-response relationship

No substance related abnormalities had been revealed on treatment of women with therapeutic doses of 2 g methenamine hippurate per day or 4 g methenamine mandelate per day during the period of pregnancy (corresponding to ca. 13 and 27 mg methenamine/kg bw/d, respectively). The observance of effects in dogs already with an oral dose of 31 mg/kg bw/d may indicate a steep dose-response relationship.

- differences in exposure (route, duration, frequency and pattern)

The estimated dermal and oral exposures with assumed absorption percentage of 50% and 100%, respectively (cf. 4.1.2.1), are compared with an oral NOAEL derived from data on the therapeutic use of the substance in humans.

- the human population to which the quantitative and/or qualitative information on exposure applies

Following the exposure pattern there is no reason to assume a special risk for children or pregnant women.

- other factors

There are no other factors known requiring a particular margin of safety.

MOS for the dermal exposure scenario

The maximum daily external exposure of consumers to methenamine from the use of cosmetics has been calculated to be 0.45 mg/kg bw/d corresponding to an internal exposure of 0.225 mg/kg bw/d. The margin of safety between the

internal exposure level of 0.225 mg/kg bw/d

and the

NOAEL (human) of 27 mg/kg bw/d

is judged to be sufficient.

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

MOS for the oral exposure scenario

An oral exposure of 0.021 mg/kg bw/d has been calculated from an assumed daily intake of 50 g provolone cheese. The margin of safety between the

exposure level of 0.021 mg/kg bw/d

and the

NOAEL (human) of 27 mg/kg bw/d

is judged to be sufficient.

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 Man exposed indirectly via the environment

The indirect exposure of humans via environment, i.e. through food, drinking water and air, is considered to be very low. Local concentrations following production and processing as intermediate have been estimated to be 0.25 mg/l and 1.0 mg/l, respectively (cf. 3.1.4.1/2). The regional concentration in water as target compartment amounts to 0.33 µg/l (cf. 3.1.8).

Data resulting from experience in humans have been used to derive NOAELs of 57 or 27 mg methenamine/kg bw/day for potential adverse effects after long-term treatment or to development, respectively. Given these values the margin of safety is judged to be sufficient. Thus, the substance is considered to be of no concern in relation to indirect exposure via the environment. This conclusion also takes into account possible adverse effects due to the formation of formaldehyde as cleavage product of methenamine in environmental compartments.

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 exposure to methenamine at the workplace and from the use of cosmetic products might result in additional body burden of up to 13 mg/person/d for concerned workers. The risk characterisation leads to the same conclusions as for occupational exposure alone.

4.2 HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES)

4.2.1 Exposure assessment

4.2.1.1 Occupational exposure

4.2.1.2 Consumer exposure

4.2.1.3 Indirect exposure via the environment

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

4.2.2.1 Explosivity

Methenamine is not explosive.

4.2.2.2 Flammability

Methenamine is highly flammable.

4.2.2.3 Oxidising potential

Due to its chemical structure, methenamine is not expected to possess oxidizing properties.

4.2.3 Risk characterisation

4.2.3.1 Workers

Methenamine is highly flammable. A risk to workers can largely be excluded in the case of proper handling in compliance with the rules for the handling of highly flammable hazardous substances.

4.2.3.2 Consumers

4.2.3.3 Man exposed indirectly via the environment

5 CONCLUSIONS / RESULTS

( ) i) There is need for further information and/or testing

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

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

Summary of conclusions:

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 releases into surface water, soil and the atmosphere. Based on the available data, methenamine represents a very low risk to the environment during all life-cycle steps considered in this report (production, processing and use).

Human Health

Workers

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

Concern is derived for skin sensitisation for all exposure scenarios. The most critical exposure scenario is scenario 2 (formulation of phenolic resin systems).

Other critical dermal toxicological endpoints are developmental toxicity and systemic toxicity after repeated contact. While for developmental toxicity concern after dermal exposure is reached for scenario 2 (formulation of phenolic resin systems), 3 (production of fuel tablets), and 4 (production of formulations used in corrosion prevention and as photo chemicals), for systemic toxicity after repeated contact conclusion iii is expressed only for the formulation of phenolic resin systems (scenario 2).

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

For the other toxicological endpoints the risk orientated conclusions result in no concern with the consequence that risk reduction measures are of low priority.

Consumers

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

Due to the skin sensitizing properties of methenamine, there is concern for the dermal exposure via cosmetic products or the use of solid fuel tablets containing methenamine.

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

This conclusion applies to all other exposure pathways and for all other toxicological endpoints.

Man exposed indirectly 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

This conclusion applies to all exposure pathways for all toxicological endpoints.

Combined exposure

From combined exposure at the workplace and via cosmetic products, the same conclusions apply as for workers alone for all scenarios and all toxicological endpoints.

Human health (risks from physico-chemical properties)

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

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APPENDIX A CALCULATION OF REGIONAL AND CONTINENTAL PEC'S

SimpleBox2.0a - Calculation of regional and continental PEC's

INPUT - Methenamine

Parameter names acc. SimpleBox20	Unit	Input	Parameter names according Euses
Physicochemical properties			
COMPOUND NAME	[-]	Methenamine	Substance
MOL WEIGHT	[g.mol^{-1}]	140,2	Molecular weight
MELTING POINT	[° C]	270	Melting Point
VAPOR PRESSURE(25)	[Pa]	0,05	Vapour pressure at 25°C
log Kow	[log10]	-4,15	Octanol-water partition coefficient
SOLUBILITY(25)	[mg.l^{-1}]	667000	Water solubility
Distribution - Partition coefficients			
- Solids water partitioning (derived from K_{oc})			
Kp(soil)	[l.kg$_d^{-1}$]	0,001456	Solids-water partitioning in soil
Kp(sed)	[l.kg$_d^{-1}$]	0,007278	Solids-water partitioning in sediment
Kp(susp)	[l.kg$_d^{-1}$]	0,007278	Solids-water partitioning in sudpended matter
- Biota-water			
BCF(fish)	[l.kg$_w^{-1}$]	1	Biocentration factor for aquatic biota
Degradation and Transfromation rates			
- Characterisation and STP			
PASSreadytest	[y / n]	n	Characterization of biodegradation
- Environmental Total Degradation			
kdeg(air)	[d^{-1}]	2,22E+01	Rate constant for degradation in air
kdeg(water)	[d^{-1}]	4,62E-02	Rate constant for degradation in bulk surface water

kdeg(soil)	[d^{-1}]	6,93E-07	Rate constant for degradation in bulk soil
kdeg(sed)	[d^{-1}]	6,93E-08	Rate constant for degradation in bulk sediment

Sewage treatment (e.g. calculated by SimpleTreat)

- Continental

FR(volatstp) [C]	[-]	0,00E+00	Fraction of emission directed to air (STPcont)
FR(effstp) [C]	[-]	1,00E+00	Fraction of emission directed to water (STPcont)
FR(sludgestp) [C]	[-]	0,00E+00	Fraction of emission directed to sludge (STPcont)

- Regional

FR(volatstp) [R]	[-]	0,00E+00	Fraction of emission directed to air (STPreg)
FR(effstp) [R]	[-]	1,00E+00	Fraction of emission directed to water (STPreg)
FR(sludgestp) [R]	[-]	0,00E+00	Fraction of emission directed to sludge (STPreg)

Release estimation

- Continental

Edirect(air) [C]	[$t.y^{-1}$]		Total continental emission to air
STPload [C]	[$t.y^{-1}$]	157	Total continental emission to wastewater
Edirect(water1) [C]	[$t.y^{-1}$]	19	Total continental emission to surface water
Edirect(soil3) [C]	[$t.y^{-1}$]	0	Total continental emission to industrial soil
Edirect(soil2) [C]	[$t.y^{-1}$]	0	Total continental emission to agricultural soil

- Regional

Edirect(air) [R]	[$t.y^{-1}$]	0	Total continental emission to air
STPload [R]	[$t.y^{-1}$]	30	Total continental emission to wastewater
Edirect(water1) [R]	[$t.y^{-1}$]	0	Total continental emission to surface water
Edirect(soil3) [R]	[$t.y^{-1}$]	0	Total continental emission to industrial soil
Edirect(soil2) [R]	[$t.y^{-1}$]	0	Total continental emission to agricultural soil

OUTPUT - Methenamine

Parameter names acc. SimpleBox20	Unit	Output	Parameter names according Euses
Physicochemical properties			
COMPOUND NAME	[-]	Methenamine	Substance
Output			
- Continental			
PECsurfacewater (total)	[mg.l^{-1}]	2,91E-05	Continental PEC in surface water (total)
PECsurfacewater (dissolved)	[mg.l^{-1}]	2,91E-05	Continental PEC in surface water (dissolved)
PECair	[mg.m^{-3}]	1,02E-15	Continental PEC in air (total)
PECagr.soil	[mg.kg$_{wwt}^{-1}$]	5,49E-11	Continental PEC in agricultural soil (total)
PECporewater agr.soil	[mg.l^{-1}]	4,62E-10	Continental PEC in pore water of agricultural soils
PECnat.soil	[mg.kg$_{wwt}^{-1}$]	5,49E-11	Continental PEC in natural soil (total)
PECind.soil	[mg.kg$_{wwt}^{-1}$]	5,49E-11	Continental PEC in industrial soil (total)
PECsediment	[mg.kg$_{wwt}^{-1}$]	1,73E-05	Continental PEC in sediment (total)
- Regional			
PECsurfacewater (total)	[mg.l^{-1}]	3,28E-04	Regional PEC in surface water (total)
PECsurfacewater (dissolved)	[mg.l^{-1}]	3,28E-04	Regional PEC in surface water (dissolved)
PECair	[mg.m^{-3}]	1,15E-14	Regional PEC in air (total)
PECagr.soil	[mg.kg$_{wwt}^{-1}$]	6,17E-10	Regional PEC in agricultural soil (total)
PECporewater agr.soil	[mg.l^{-1}]	5,19E-09	Regional PEC in pore water of agricultural soils
PECnat.soil	[mg.kg$_{wwt}^{-1}$]	6,17E-10	Regional PEC in natural soil (total)
PECind.soil	[mg.kg$_{wwt}^{-1}$]	6,17E-10	Regional PEC in industrial soil (total)
PECsediment	[mg.kg$_{wwt}^{-1}$]	1,98E-04	Regional PEC in sediment (total)

The report provides the comprehensive risk assessment of the substance methenamine. It has been prepared by Germanyin 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.

Part I - Environment

This part of the evaluation considers the emissions and the resulting exposure to the environment 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.

The environmental risk assessment concludes that there is no concern for any of the compartments.

Part II – Human Health

This part of the evaluation considers the emissions and the resulting exposure to human populations in all life cycle steps. The scenarios for occupational exposure, consumer exposure and humans exposed via the environment have been examined and the possible risks have been identified.

The human health risk assessment concludes that there is concern for workers and consumers, but not for humans exposed via the environment.

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) N. 793/93.