

# **METHENAMINE**

CAS No: 100-97-0

EINECS No: 202-905-8

## **SUMMARY RISK ASSESSMENT REPORT**

*Final report, 2008*

Germany

***FINAL APPROVED VERSION***

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## **PREFACE**

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

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

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<sup>1</sup> European Chemicals Bureau – Existing Chemicals – <http://ecb.jrc.it>



# CONTENTS

1	GENERAL SUBSTANCE INFORMATION .....	3
1.1	IDENTIFICATION OF THE SUBSTANCE.....	3
1.2	PURITY/IMPURITIES, ADDITIVES .....	4
1.3	PHYSICO-CHEMICAL PROPERTIES.....	4
1.4	CLASSIFICATION .....	5
2	GENERAL INFORMATION ON EXPOSURE .....	6
3	ENVIRONMENT.....	7
3.1	ENVIRONMENTAL EXPOSURE .....	7
3.2	EFFECTS ASSESSMENT .....	8
3.3	RISK CHARACTERISATION .....	9
4	HUMAN HEALTH.....	12
4.1	HUMAN HEALTH (TOXICITY) <b>ERROR! BOOKMARK NOT DEFINED.</b>	
4.1.1	Exposure assessment <b>Error! Bookmark not defined.</b>	
4.1.2	Effects assessment <b>Error! Bookmark not defined.</b>	
4.1.3	Risk characterisation <b>Error! Bookmark not defined.</b>	
4.2	HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES) <b>ERROR! BOOKMARK NOT DEFINED.</b>	
5	RESULTS.....	31
5.1	ENVIRONMENT .....	31
5.2	HUMAN HEALTH .....	31
5.2.1	Human health (toxicity).....	31
5.2.2	Human health (risks from physico-chemical properties).....	32

# TABLES

Table 1.1	Summary of physico-chemical properties.....	4
Table 3.1	PEC/PNEC ratios for the aquatic compartment .....	9



# 1

## GENERAL SUBSTANCE INFORMATION

### 1.1

#### IDENTIFICATION OF THE SUBSTANCE

CAS Number: 100-97-0  
EINECS Number: 202-905-8  
IUPAC Name: 1,3,5,7-Tetraazatricyclo-[3.3.1.1(3.4)] -decane  
Synonyms: Hexamethylenetetramine

Methenamine,

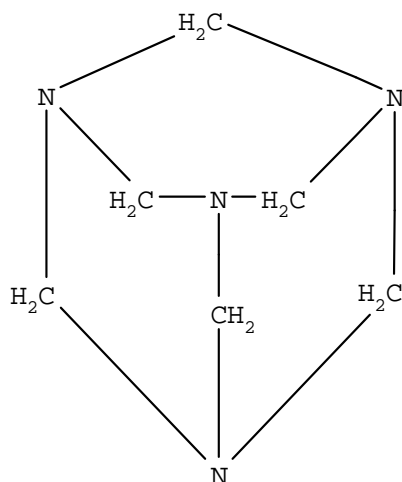
Urotropin,

Formin

Molecular weight: 140.2 g/mol

Molecular formula:  $C_6H_{12}N_4$

Structural formula:



## 1.2 PURITY/IMPURITIES, ADDITIVES

Purity: 99 - 99.5 % w/w

Impurities: < 0.5 % water

Additives: 1.5 - 4% paraffine oil  
0.5 - 3% amorphous silic

## 1.3 PHYSICO-CHEMICAL PROPERTIES

**Table 1.1** Summary of physico-chemical properties

Physical state	at 20 °C, 1013 hPa: white crystalline powder or colorless lustrous crystals
Melting point	> 270 °C; from 230 °C sublimation
Boiling point	n.a.
Relative density	1.331 at -5 °C
Vapour pressure	0.0005 hPa at 20 °C
Surface tension	70.4 mN/m
Water solubility	667 g/l at 25 °C
Partition coefficient, $\log_{\text{KOW}}$	- 4.15 (calculated)
Flash point	not determined
Flammability	highly flammable
Ignition temperature	245 °C
Explosive properties	not explosive
Oxidising properties	no oxidising properties
Henry constant	$1.051 \cdot 10^{-5} \text{ Pa} \cdot \text{m}^3/\text{mol}$



Dissociation constant	8.4
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#### **1.4 CLASSIFICATION**

Classification:

F, R11

R 42/43

Labelling:

F, Xn

R: 11-42/43

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

## 2

## GENERAL INFORMATION ON EXPOSURE

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. 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 recent years some of the production sites were closed, companies were sold or merged and structures and responsibilities changed.

In 2001 the following companies were main producers or importers of methenamine in the EU (EU<sub>15</sub>):

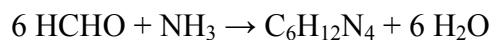
Bakelite Italia S.p.A. (I)

Caldic Chemie B.V. (NL)

INEOS Paraform GmbH (formerly Degussa AG, DE)

As realistic worst case, a production volume of 30,000 tonnes is assumed for the European market (EU<sub>15</sub>) and used for the exposure estimations in this report.

The production of methenamine can be performed according to the continuous Meissner-process in a closed system. The substance is obtained by the reaction of formaldehyde and ammonia in the aqueous phase under reduced pressure at approx. 40 - 90 °C.



In two alternative processes the reaction takes place either in the gaseous phase or in an inert solvent.

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.

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. 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. An amount of approximately 3 % is used as chemical intermediate in nitration reactions, e.g. in the production of explosives like Hexogen and Octogen. Approximately 2 % is used as fuel tablets for camping stoves (consumer product). Additional uses are mentioned in the literature. Since these applications contribute < 1 % of the methenamine use in total they were not considered for the exposure estimation.

## 3 ENVIRONMENT

### 3.1 ENVIRONMENTAL EXPOSURE

#### 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.

Environmental releases are neither expected from residual contents due to complete decomposition during processing nor from products (fuel tablets) as the tablets are burned without residues.

#### Environmental fate

Direct photolysis is not expected. Under atmospheric conditions methenamine has a half live of 45 min (rate constant of  $0.87 \times 10^{-10} \text{ cm}^3 \text{ molecules}^{-1} \text{ s}^{-1}$ ) due to reaction with the OH radical.

Methenamine is susceptible to hydrolysis if protonated. Methenamine has a  $\text{pK}_a$  of 8.4 The half-life increases with increasing of the pH. 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  $\text{pH} > 7$ . 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, and degradation might be supported by microbial activity.

The degree of biodegradation varies strongly. 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.

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.

Methenamine is highly water soluble (667g/l).

A Henry's law constant of  $1.051 \times 10^{-5} \text{ Pa} \cdot \text{m}^3 \cdot \text{mol}^{-1}$  indicates that the substance is non-volatile from an aqueous solution.

The  $K_{OC}$  of 0.073 l/kg is calculated using a log  $K_{ow}$  of -4.15. This indicates no potential for geoaccumulation.

According to Mackay model (level 1) the hydrosphere is the target compartment of methenamine (100%) in the environment.

The  $K_{OW}$  value of -4.18 does not indicate a potential for bioaccumulation.

### Environmental concentrations

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. The estimated  $C_{\text{local}}$  is 0.25 mg/l. Continental and regional concentrations are estimated according to the methods of the TGD and assuming a realistic worst case, the complete EU production volume of 30,000 t/a. The estimated PEC are as follows:

$$\text{PEC}_{\text{regional water}}: \quad 3.3 * 10^{-4} \text{ mg/l}$$

$$\text{PEC}_{\text{continental water}}: \quad 2.9 * 10^{-5} \text{ mg/l}$$

According to the physico-chemical properties methenamine is not expected to be distributed into sediment in relevant amounts and an estimation of the exposure for this compartment is therefore dispensable.

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.

## **3.2 EFFECTS ASSESSMENT**

### Aquatic compartment

Short-term results are available for organisms representing two trophic levels in fresh and brackish water. The relevant  $LC_{50}$ -/ $EC_{50}$ -values are in the range of 36 g/l (daphnia) to 92 g/l (crustacean) and  $LC_{50}$  values ranging between 41 to 49.8 g/l (fish).

A 14 d  $E_rC_{50}^2$  of 3g/l estimated from the growth curves was established for algae. According to the TGD an assessment factor of 1000 should be used as long term values for fish and invertebrates are missing.

$$\text{PNEC}_{\text{water}} = 3 \text{ mg/l}$$

When reaching the aqueous environment, methenamine is degraded hydrolytically to ammonium and formaldehyde. The rate of hydrolysis is strongly pH-dependent. These two degradation products are generally an order of magnitude more toxic. For formaldehyde acute  $EC_{50}$  values range between 0.46 mg/l (invertebrates) and 1020 mg/l (fish) and for ammonia between 0.1 mg/l (fish) and 5 mg/l (invertebrates). Long term NOEC values for fish and invertebrates are approximately 0.02-0.1 mg/l. Algae are comparatively insensitive with an  $EC_{50}$  ranging between 1-10 mg/l after an exposure time of 72 to 120 hours. This may be due to the fact that algae can use ammonia as a nitrogen source.

The environmental levels of formaldehyde due to the degradation of methenamine are very low compared to the formaldehyde production itself with 5–6 millions t/a. 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.

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<sup>2</sup>  $E_rC$  ist the effective concentration with regard to the endpoint growth rate of the algae population

Ammonia is naturally 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 preferred to assess the risks of formaldehyde and ammonia in a separate risk assessment addressing the complete situation for these substances.

#### Terrestrial compartment

Reliable data about the effects on terrestrial organisms are not available. However, no relevant exposure of the terrestrial compartment is to be expected and the risk for terrestrial organisms is considered to be low.

#### Secondary poisoning

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.

#### Toxicity to microorganisms

Only one test with microorganisms is available that can be used for the risk assessment. The inhibition of nitrification by methenamine was tested. 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.

A tentative  $PNEC_{wwtp}$  may be derived based on this NOEC. According to the TGD an assessment factor of 1 has to be applied. Therefore:

$$PNEC_{wwtp} = 100 \text{ mg/l}$$

### **3.3 RISK CHARACTERISATION**

#### 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 3.4.

To characterise the risk following production, the volume released by this site and the  $C_{local}$  as determined was taken into account. The estimated  $C_{local}$  is 0.25 mg/l. Adding a background concentration ( $PEC_{regional}$ ) of 0.00033 mg/l, the resulting  $PEC_{local}$  for this realistic worst-case production site is 0.25 mg/l.

**Table 3.1 PEC/PNEC ratios for the aquatic compartment**

Process	Data	Scenario	PEC <sub>local</sub> (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)**

The hydrolytical degradation products, formaldehyde and ammonia, are acutely more toxic for aquatic organisms. However, the contribution to the environmental levels due to degradation of methenamine are very low. The situation for formaldehyde and ammonia should be considered in separate risk assessments.

#### Atmosphere

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)**

#### Terrestrial compartment

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. The substance is degraded quickly in the air and transport via air is unlikely. Hence, this pathway of exposing the terrestrial compartment is negligible. 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)**

#### 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. **Conclusion (ii)**

#### PBT assessment

The logK<sub>OW</sub> calculated is -4.2 indicating no potential for bioaccumulation (logK<sub>OW</sub> < 4.5).

No information concerning long-term effects is available. In the acute tests methenamine was non-toxic to aquatic organisms. Taking the information about degradability and acute effects

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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)**

## **4 HUMAN HEALTH**

### **4.1 HUMAN HEALTH (TOXICITY)**

#### **4.1.1 Exposure assessment**

##### Occupational exposure

Methenamine is produced in the EU with a total production capacity of about 30.000 t in 2001.

Based on the available information, 95 % of the produced methenamine is used at the production of powdery or liquid preparations of phenolic resins and phenolic resins moulding compounds. 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. 2 % of the produced methenamine is further processed to fuel tablets (contains 97 % methenamine). And the last 3% are used as a chemical intermediate in nitration reactions (e.g. production of explosives).

Detailed information on the production volumes and the use of methenamine is given in chapter 2.

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

- Production of methenamine and further processing to explosives
- Formulation of phenolic resin systems
- Production of fuel tablets
- Formulation of preparations (e.g. used for corrosion prevention and as photochemicals)
- Use of products containing phenolic resin systems.

In the literature further uses as corrosion inhibitors, as photochemicals, as fertilisers, as fungicides, as limestone removers, as carpet cleaners, as human medicines or as preservatives in paints, leather and cosmetics are mentioned. The possible exposure during the use of this kind of preparations is not described in this exposure assessment, 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 occupational exposure limit in Sweden, Norway and Iceland amounts to 3 mg/m<sup>3</sup> (TLV, Ariel, 2007). OELs do not exist in the other EU member states or in the USA.

The exposure assessment is based on measured data and literature data, expert judgement and estimations according to the EASE model (Estimation and Assessment of Substance Exposure). The exposure levels should be regarded as reasonable worst case estimates representing the highly exposed workers.

Methenamine is a colourless, crystalline substance which decomposes under the effect of heat (decomposition temperature 200 °C). Low-dust powders are obtained by addition of paraffin. Due to the physico-chemical properties of methenamine (solid, vapour pressure 0.05 Pa) inhalation and dermal exposure to dust during the handling of the powdery substance (during the production and formulation) or powdery preparations (phenolic resin systems containing 15 % methenamine) are expected to be the main source of exposure.



Measurement results concerning inhalation exposure were only available for the production. The data basis is sufficient to be regarded as representative. For the scenarios “Formulation of phenolic resin systems” and “Production of formulations (e.g. used for corrosion prevention and as photochemical)”, analogous data were taken into account.

The produced 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.

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. At the formulation of phenolic resin systems an analogy exposure scenario, dumping of powders in a formulation company, is taken. For other sectors, exposure levels are assessed for the unprotected worker based on the assumption that gloves are irregularly worn.

### Summary of exposure data

Exposure scenario	Duration and frequency of activities relevant for exposure	Inhalation exposure Shift average [mg/m <sup>3</sup> ]	Dermal exposure Shift average [mg/p/day]
1. Production and further processing to explosives (with LEV)	shift length, daily	1 a) 4.0 (dusty material, highest measurement)	4.2 (with gloves)
		1 b) 0.2 (low dust material)	
2. Formulation of phenolic resin systems	shift length, daily	12 (analogous data)	3000 (analogous data)
3. Production of fuel tablets (97 % methenamine)	shift length, 80 days/year	5 (EASE, with LEV)	420 (EASE, without gloves)
4. Production of formulations (e.g. used for corrosion prevention and as photochemical)	1 h/shift, daily	1 (analogous data)	420 (EASE, without gloves)
5. Use of phenolic resin systems (up to 15 % methenamine)	shift length, daily	7.5 (EASE, without LEV)	126 (EASE, without gloves)

### 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 coffee machines (< 1%) and in two Steam Vac floor and carpet/upholstery cleaners (< 1%). In one case methenamine is used in the pure form in solid fuel. The substance is present as preservative 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 to methenamine may be derived from its use in limestone removers, cleaners, solid fuel tablets, and cosmetic products.

From the use of limestone removers for coffee machines occasional short-time dermal exposure may occur in connection with the handling of the limestone remover during use. Considering the small contact area (parts of the hands) and the short contact time, the dose of methenamine available to systemic absorption during this use may be considered negligible.

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 resulting in residual amounts of the substance in the textile. The amount of methenamine migrating from upholstered furniture to the skin was estimated as 3000 µg per year, corresponding to an average external dermal exposure of 0.14 µg/kg bw/d. This amount can be neglected in relation to the amount by other exposure pathways.

Dermal exposure to methenamine for short times may occur repeatedly during the application (handling/breaking) of solid fuel tablets containing the substance in high concentrations (>95%).

The main source of dermal consumer exposure to methenamine is the use of the substance in cosmetic products such as lotions, creams or 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%. It may be used in higher concentrations for other specific purposes, but no information is available on such uses. The estimation of external dermal exposure to methenamine via cosmetics, based on the SCCNFP approach (SCCNFP/0321/00, Final), amounts to 26.68 mg/person/d or 445 µg/kg bw/d in a worst-case scenario, assuming the consumer would use a set of cosmetic products amounting to a total of 17.79 g that contain the same preservative.

### *Oral exposure*

According to § 28 of the German cheese-directive, methenamine is allowed as preservative in provolone cheese in a quantity of 25 mg/kg (calculated as formaldehyde). It is not allowed in other food. From a maximum daily intake of 50 g provolone cheese (99th percentile of the estimated daily consumption quantity) a possible oral intake of 1.25 mg of methenamine per day per person might result (external exposure). With an assumed absorption rate of 100%, this leads to an internal exposure of 0.021 mg/kg bw /d.

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.

#### Humans exposed via the environment

Releases of methenamine into the environment following production, formulation and processing were calculated in chapter 3. The target compartment is water, a release into air can be widely excluded. The indirect exposure of humans via the 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. Its degradation products are ammonium and formaldehyde. In view of a total production volume of formaldehyde of 5-6 million t/a, its formation from methenamine would contribute little to a possible overall risk from formaldehyde, which is not assessed in the present report.

#### Combined exposure

For the consideration of combined exposure, occupational exposure in combination with dermal exposure via cosmetic products might be relevant.

### **4.1.2 Effects assessment**

#### Toxicokinetics, metabolism and distribution

After oral uptake in man, methenamine is rapidly absorbed from the intestines. 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. Under acidic conditions, hydrolytic cleavage of methenamine to the ammonium and formaldehyde can occur. At the acidic pH of the stomach, 10-20% of an orally ingested dose are hydrolysed. 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 further oxidised to carbon dioxide and water or excreted via the kidneys. Most of the rest of an oral methenamine dose is excreted unchanged in the urine within 12 h.

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.

### Acute toxicity

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. 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.

### Irritation

Methenamine is not a local irritant by contact with skin or eyes of rabbits. In humans there is some but inconclusive evidence for local skin irritation after occupational exposure, which might be due to the hydrolysis to formaldehyde and ammonia at the acidic pH of the sweat.

### Corrosivity

Methenamine has no corrosive properties.

### Sensitisation

Guinea pigs exhibited strong skin sensitization in a maximization test with a 50% aqueous solution of the substance. In a Local Lymph Node Assay (LLNA) a positive effect concentration (EC3) of 30.6% methenamine was derived – comparable to the EC3 for formaldehyde which was determined in the same study (giving rise to the speculation whether formaldehyde, which may be generated by hydrolysis of methenamine upon contact to skin, and not methenamine itself is the main causative agent of the observed effects). Skin sensitizing properties of methenamine have also been described in humans in several reports.

Earlier reports included a number of cases where allergic symptoms of the respiratory system, such as wheezing and asthma, occurred upon methenamine exposure. However, in all cases exposure to other irritant and sensitizing chemicals occurred simultaneously. The respiratory hypersensitivity could not specifically be related to methenamine. A well-documented recent study, which was designed to analyse the sensitizing potential of methenamine, gave no evidence that occupational exposure to methenamine alone may cause respiratory sensitization.

### Repeated dose toxicity

There are no oral repeated dose toxicity studies in experimental animal according to the current regulatory requirements or of equivalent quality. A number of older diet, gavage and drinking water studies in several animal species are reported. None of these studies provided data on hematology and clinical chemistry; data on histopathology were limited. In these studies, methenamine did not cause any toxic effects in rats and mice up to and including 2.5 g/kg bw/d. In-life parameters, which included body weight gain, food consumption, and survival, were unaffected. 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 (it may be a consequence of a reaction between formaldehyde in the urine and kynurenine, a normal constituent in the rat hair). Post mortem analyses, which included organ weights, gross pathology and histopathology, revealed no abnormalities. Lifetime exposure of cats to 60.65 mg/kg bw/d methenamine in the diet did not induce relevant toxic effects. 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. There were no animal studies on repeated dose toxicity of methenamine after inhalation.

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 complications were observed in patients receiving methenamine as an urinary antibacterial-antiseptic at dose levels of 2 - 4 g/d (corresponding to a NOAEL of 57 mg/kg bw/d) for up to 4 weeks. Higher doses of 8 g/d (corresponding to a LOAEL of 114 mg/kg bw/d) for 3 - 4 weeks induced urological abnormalities such as bladder irritation, painful and frequent micturition, albuminuria, and hematuria.

#### Mutagenicity

Methenamine was weakly positive in bacterial gene mutation assays at extremely high concentrations and in an in vitro chromosomal aberration assay. According to these results 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.

#### Carcinogenicity

There are no animal studies available 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 studies, 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.

The major metabolite of methenamine, formaldehyde, was investigated in a valid cancer study with administration to rats via the drinking water which 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.

Cell transformation data are available from a Stiles' cell transformation assay using BHK-21/cl.13 cells. An increase in the transformation rate was observed after exposure to methenamine in a concentration of 1000 µg/ml. However, this test system is not validated and the methodology was insufficiently documented.

Data on humans occupationally exposed to methenamine alone for a long time are not available. Retrospective and prospective epidemiology studies included workers in the steel foundry and in the tire and rubber industrie, who were exposed to mixtures of chemicals including methenamine together with several other substances of suspected carcinogenic potential. These studies revealed an overall increase in the mortality from cancer, mainly due to an excess number of deaths from lung and bladder cancer. 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, the observed increased cancer risks could not be conclusively attributed to the exposure to one particular substance. 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.

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

#### Toxicity for reproduction

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.

Treatment-associated developmental toxicity was observed in rats (at high dosages) as well as in beagle dogs. The effects concerned postnatal development in terms of pre-weaning mortality and postnatal growth retardation. As NOAEL/developmental toxicity a value of 100 mg/kg bw/d was derived for rats and a value of 15 mg/kg bw/d for dogs.

Human data on potential adverse effects on development are available from the examination of women who were treated with methenamine salts during pregnancy (Furness et al., 1974). After 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) there was no indication of a specific impairment of pregnancy outcome or of the development of the children.

### **4.1.3 Risk characterisation**

#### Workers

##### **Introduction to occupational risk assessment**

There are five relevant occupational exposure scenarios for methenamine which are described and discussed in section 4.1.1. The exposure routes to be considered in connection with the workplace are exposure by inhalation or dermal contact to dusts during the handling of the powdery substance or powdery preparations.

Relevant human toxicity data are available, because methenamine is used for the prevention of recurrent urinary infections in man. Repeated dose toxicity, developmental toxicity and sensitisation might be addressed as the most significant effects in the toxicological profile of methenamine.

Concerning the oral route 100% systemic availability of methenamine or its metabolites can be assumed (experimental data). The systemic availability after dermal exposure is assumed to be 50%, whereas the value after inhalation is set at 100% (both are default values).

In table 4.1.3.A the exposure levels are summarised and the route specific and total internal body burden is identified.

**Table 4.1.3.A: Methenamine exposure levels which are relevant for occupational risk assessment and internal body burden**

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

<sup>(1)</sup> based on the assumption of 100% inhalative absorption; breathing volume of 10 m<sup>3</sup> per shift

<sup>(2)</sup> based on the assumption of 50% systemic availability of methenamine after dermal contact

<sup>(3)</sup> measurement data

<sup>(4)</sup> EASE-estimation

<sup>(5)</sup> analogous data

<sup>(6)</sup> 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 studies and workplace exposure levels. Scientifically based adjustment factors are used for the stepwise extrapolation of animal data to the worker population (e.g. adaption of scenarios, route-to-route extrapolation, inter- and intraspecies extrapolation and duration adjustment). The multiplicative combination of these different factors yield the minimal MOS value as a decision mark for concern. Minimal MOS values may be different for each toxicological endpoint.

In a parallel procedure, which gives identical but more direct results, a “critical exposure level” (quotient of experimental NOAEL and the according minimal MOS) is identified for each endpoint, indicating concern if occupational exposure levels exceed this value. In the following risks at the workplace are considered specifically for each toxicological endpoint.



## Acute Toxicity

### *Local effects*

*see irritation, no further information available*

### *systemic effects*

**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

## Acute toxicity by 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<sup>3</sup> (20,000 mg/kg x 70 kg / 10 m<sup>3</sup>). The highest inhalative exposure level of 12 mg/m<sup>3</sup> results from scenario 2 (formulation of phenolic resin systems). The according MOS value of 11,700 (starting point 140,000 mg/m<sup>3</sup> / exposure of 12 mg/m<sup>3</sup>) is considered to be high enough to exclude acute toxic effects at these exposure conditions.

## Acute toxicity by dermal and combined 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 2,000 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 evaluation might be backed by the human data on repeated oral toxicity where 8,000 mg/person/day for some weeks produced side effects in humans. 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, relevant acute dermal risks are not anticipated to occur. This applies also for combined exposure.

## **Irritation/Corrosivity**

**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

### ***Dermal and eye irritation***

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.

## **Sensitisation**

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

### ***Skin sensitisation***

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.

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.

### ***Respiratory sensitisation***

**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

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 with methenamine, there was no evidence that methenamine alone may cause respiratory sensitisation after occupational exposure.

## Repeated dose toxicity

### *Local effects by inhalation and dermal contact*

**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

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.

Limited information results from a subchronic 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.

### *Systemic effects by inhalation, dermal contact and combined exposure*

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

Relevant human or experimental data on dermal or inhalation toxicity are not available. 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 2,500 mg/kg/day.

From the use of methenamine for the prevention of recurrent urinary infections in man it is known that dose levels of 2,000 to 4,000 mg/day (equivalent to about 28 to 57 mg/kg bw/day) produced no harmful reactions or complications. Therapeutic doses of 8,000 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) and is used for risk characterisation.

Because of 100% oral absorption, the internal starting point is 4,000 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<sup>3</sup> (4,000 mg/person/day / 10 m<sup>3</sup>/day). For dermal absorption a percentage of 50% is taken forward. This results in an external starting point for dermal contact of 8,000 mg/person/day.

The minimal MOS consists of a factor of 5/7 for the adaptation of scenarios (therapeutic use 7 days/week to 5 days/week for workers), a factor of 6 for duration adjustment ("subacute" to chronic) and a factor of 3 to account for intraspecies differences (this factor is lowered, because the assumption is made, that the exposed group of persons does contain individuals, who are more sensitive than the average of the individuals. This leads to a factor lower than 5). The multiplication of these factors gives a minimal MOS of ~13 (5/7 x 6 x 3).

The corresponding critical exposure levels are calculated as 31 mg/m<sup>3</sup> for inhalation (400 mg/m<sup>3</sup> / 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).

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.

### **Mutagenicity**

**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

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.

### **Carcinogenicity**

**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

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.

### **Reproductive toxicity**

#### ***Fertility impairment***

**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

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. Because there is no indication for adverse fertility effects, a MOS approach is not performed.

### ***Developmental toxicity***

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

No substance related abnormalities during pregnancy or development of the children had been revealed from investigations on women that had been treated with methenamine salts during pregnancy. 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.

In opposite to the human data, treatment associated developmental effects were shown for experimental animals in a study which does not sufficiently meet the test requirements. In this study effects were observed in beagle dogs during the postnatal period of development in terms of preweaning mortality and postnatal growth retardation. As NOAEL/developmental toxicity a value of 15 mg/kg bw/d was derived.

Although there were no effects in treated pregnant women observed, a MOS calculation is done, because the dog data 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<sup>3</sup> (1890 mg/person/day / 10 m<sup>3</sup>).

The minimal MOS consists of a factor of 3 to account for intraspecies differences (for justification see also under repeated dose toxicity) and a factor of 3 to consider the severity of possible developmental effects. Altogether the minimal MOS calculates to 9 (3 x 3).

The corresponding critical exposure levels are calculated as 21 mg/m<sup>3</sup> for inhalation (189 mg/m<sup>3</sup> / 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).

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.

### **Summary of occupational risk assessment**

In table 4.1.3.B occupational exposure scenarios are listed to give an overview for all exposure situations with concern. For methenamine concern results from dermal contact to the

substance (skin sensitisation, developmental toxicity and systemic effects after repeated dermal contact).

**Table 4.1.3.B: Endpoint-specific overall conclusions for methenamine**

Toxicological endpoints		general conclusion	exposure scenarios
Acute toxicity	inhalation	ii	
	dermal	ii	
	combined	ii	
Irritation/ Corrosivity	dermal	ii	
	eye	ii	
	acute respiratory tract	ii	
Sensitisation	skin	iii	all five scenarios
	respiratory	ii	
Repeated dose toxicity	local, inhalation	ii	
	local, dermal	ii	
	systemic, inhalation	ii	
	systemic, dermal	iii	2
	systemic, combined	iii <sup>(1)</sup>	2
Mutagenicity		ii	
Carcinogenicity	inhalation	ii	
	dermal	ii	
	combined	ii	
Fertility impairment	inhalation	ii	
	dermal	ii	
	combined	ii	
Developmental toxicity	inhalation	ii	
	dermal	iii	2, 3, 4
	combined	iii <sup>(1)</sup>	2, 3, 4

<sup>1)</sup> conclusion iii already results from dermal exposure, therefore it does not seem specific for combined exposure scenarios

In table 4.1.3.C 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 4.1.3.C: 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 photochemicals	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

### Consumers

Methenamine is used as a component of cosmetics resulting in external dermal exposures up to 0.45 mg/kg bw/d corresponding to internal exposures of 0.225 mg/kg bw/d. To some extent, local skin contact 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). Dermal contact is considered the most important route of potential consumer exposure.

### *Acute Toxicity*

Human data on acute toxicity are not available. From limit tests with rats, it is known that the LD50 values for dermal and oral exposure are above 2 g/kg bw and 20 g/kg bw, respectively (no symptoms of toxicity were observed). According to the exposure assessment, consumers are exposed to methenamine via the oral and dermal route in concentrations several orders of magnitude lower than those tested in toxicity tests in animals. Therefore, the substance is of no concern for the consumer in relation to acute toxicity. **Conclusion (ii)**

### *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. The available data base does not warrant a classification of methenamine as “irritant”. Additionally, it is taken into account that risk reduction measures, which are to be proposed due to concern from skin sensitizing properties, will also protect against potential skin irritation. **Conclusion (ii)**

### *Corrosivity*

Methenamine did not show local corrosivity. **Conclusion (ii)**

#### *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. Dermal exposure of consumers to methenamine is primarily expected from the use as ingredient in cosmetic products. As a preservative, a maximum level of 0.15% is allowed; higher concentrations in cosmetics are permitted for other specific purposes. Brief local skin contact may also occur from the use of solid fuel tablets. Even at low concentrations or after brief contact, it cannot be excluded that skin sensitization will occur. **Conclusion (iii)**

#### *Repeated dose toxicity*

No complications were observed in patients receiving methenamine as an urinary antibacterial-antiseptic at dose levels of 2 - 4 g/d for up to 4 weeks (corresponding to a NOAEL value of 57 mg/kg bw/d). 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 oral 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. The NOAEL of 57 mg/kg bw/d, derived from experience in humans by the oral route, is considered to be the most appropriate value for risk assessment. Even though there is no study available which is performed in accordance with internationally recognized guidelines and GLP standards, the overall information derived from all studies is not contradictory so that a judgement can be based on this database. Since the risk assessment can be based on human data, considerations on interspecies variations are not necessary. Following the exposure pattern there is no reason to assume a special risk for children, elderly, or pregnant women. There are no reasons to assume a special extent of uncertainty which has to be taken into account or any other factors that would require an extra margin of safety.

The margin of safety between the internal exposure level of 0.225 mg/kg bw/d resulting from the dermal application of methenamine in cosmetics and the NOAEL (human) of 57 mg/kg bw/d is judged to be sufficient. **Conclusion (ii)**

The margin of safety between the exposure level of 0.021 mg/kg bw/d resulting from oral intake of methenamine in provolone cheese and the NOAEL (human) of 57 mg/kg bw/d is judged to be sufficient. **Conclusion (ii)**

#### *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)**

#### *Carcinogenicity*



Several cohort and mortality studies are available among workers, who were exposed to methenamine contained in mixtures with several other chemicals of suspected carcinogenic potential. Even though in these studies an excess incidence of lung and bladder tumours was noted among the workers, there was no clear evidence for a causal relationship between specific cancer mortality and exposure to methenamine. With respect to the use of methenamine a pharmaceutical, there is no information on the formation of tumours. A number of long-term oral (gavage, feeding, drinking water) studies in experimental animals, using a variety of strains of rats and mice, some involving high dose levels up to and including 2.5 g/kg bw/d gave no firm indication of carcinogenic effects. None of these studies fully meets modern protocols for carcinogenicity studies. Nonetheless, in the light of negative *in vivo* mutagenicity tests, concern is not to be expected. **Conclusion (ii)**

#### *Toxicity for reproduction*

High dose levels of methenamine (> 1000 mg/kg bw/d) were investigated in several older studies on reproductive toxicity in rats which give no indication of an overt toxic potential of methenamine adverse to reproductive performance or capability. From these studies a NOEL/fertility value of 1.5 g/kg bw/d is derived.

The margin of safety between the dermal exposure of 0.225 mg/kg bw/d from the use of cosmetics (internal exposure, calculated from the external exposure of 0.45 mg/kg bw/d) and the NOEL/fertility (rat) of 1500 mg/kg bw/d is judged to be sufficient. **Conclusion (ii)**

The margin of safety between the assumed oral exposure of 0.021 mg/kg bw/d from the intake of provolone cheese and the NOEL/fertility (rat) of 1500 mg/kg bw/d is judged to be sufficient. **Conclusion (ii)**

Treatment-associated developmental toxicity (increased pre-weaning mortality and postnatal growth retardation) was observed in rats (at high dosages) as well as in beagle dogs. NOAEL/developmental toxicity values were derived as 100 mg/kg bw/d for rats and as 15 mg/kg bw/d for dogs. Human data on potential adverse effects on development, derived from women who were orally treated with methenamine salts during pregnancy, revealed no substance-related abnormalities with regard to the course of pregnancy or the development of the children. The corresponding NOAEL/dev. tox. (human) of 27 mg methenamine/kg bw/d (calculated from the therapeutic administration of 2 g/d methenamine hippurate or 4 g/d methenamine mandelate) seems more appropriate for the risk assessment than the available animal data of limited quality. In using data directly derived from human experience considerations on interspecies variations are not necessary. There is indication that dogs are more susceptible to methenamine than rats. Given that in humans no substance related abnormalities resulted after intake of 27 mg methenamine/kg bw/d, the observed effects in dogs already at 31 mg/kg bw/d may also indicate a steep dose-response relationship. Following the exposure pattern there is no reason to assume a special risk for children or pregnant women. There are no other factors known requiring a particular margin of safety.

The margin of safety between the maximum dermal exposure of 0.225 mg/kg bw/d from the use of cosmetics (internal exposure, calculated from 0.45 mg/kg bw/d external exposure) and the NOAEL/dev. tox. (human) of 27 mg/kg bw/d is judged to be sufficient. **Conclusion (ii)**

The margin of safety between the assumed oral exposure level of 0.021 mg/kg bw/d from the intake of provolone cheese and the NOAEL/dev. tox. (human) of 27 mg/kg bw/d is judged to be sufficient. **Conclusion (ii)**

### Humans exposed 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. The regional concentration in water as target compartment amounts to 0.33 µg/l.

From data obtained from experience in humans NOAEL values of 57 and 27 mg methenamine/kg bw/day were derived for potential repeated dose toxicity and developmental toxicity, respectively. The margin of safety between these values and the estimated environmental exposure 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).**

### 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)**

## 5 RESULTS

### 5.1 ENVIRONMENT

#### 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).

### 5.2 HUMAN HEALTH

#### 5.2.1 Human health (toxicity)

##### Workers

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

This conclusion applies to 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 and no need 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.

This conclusion applies to the dermal exposure via cosmetic products or the use of solid fuel tablets containing methenamine due to its skin sensitizing properties.

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

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

#### Humans exposed via the environment

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

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.

### **5.2.2 Human health (risks from physico-chemical properties)**

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

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The report provides the summary of the comprehensive risk assessment of the substance methenamine. It has been prepared by Germany in the frame of Council Regulation (EEC) No. 793/93 on the evaluation and control of the risks of existing substances, following the principles for assessment of the risks to humans and the environment, laid down in Commission Regulation (EC) No. 1488/94.

#### 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.