EUROPEAN COMMISSION

Health & Consumer Protection
Directorate-General

Scientific Committee on Health and Environmental Risks

SCHER

Risk Assessment Report on Methenamine

Human Health Part

CAS No.: 100-97-0
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Scientific Committees
on consumer products
on emerging and newly identified health risks
on health and environmental risk

The SCHER adopted this opinion at its 16th plenary on 23 April 2007

About the Scientific Committees

Three independent non-food Scientific Committees provide the Commission with the scientific advice it needs when preparing policy and proposals relating to consumer safety, public health and the environment. The Committees also draw the Commission's attention to the new or emerging problems which may pose an actual or potential threat.

They are: the Scientific Committee on Consumer Products (SCCP), the Scientific Committee on Health and Environmental Risks (SCHER) and the Scientific Committee on Emerging and Newly-Identified Health Risks (SCENIHR) and are made up of external experts.

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SCHER

Questions relating to examinations of the toxicity and ecotoxicity of chemicals, biochemicals and biological compound whose use may have harmful consequences for human health and the environment.

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1. BACKGROUND

Council Regulation 793/93 provides the framework for the evaluation and control of the risk of existing substances. Member States prepare Risk Assessment Reports on priority substances. The Reports are then examined by the Technical Committee under the Regulation and, when appropriate, the Commission invites the Scientific Committee on Health and Environmental Risks (SCHER) to give its opinion.

2. TERMS OF REFERENCE

On the basis of the examination of the Risk Assessment Report the SCHER is invited to examine the following issues:

(1) Does the SCHER agree with the conclusions of the Risk Assessment Report?

(2) If the SCHER disagrees with such conclusions, it is invited to elaborate on the reasons.

(3) If the SCHER disagrees with the approaches or methods used to assess the risks, it is invited to suggest possible alternatives.

3. OPINION

3.1 General comments

The document is written in accordance with the requirements of the TGD; all relevant endpoints are addressed. The SCHER agrees with the proposed conclusions. However, the SCHER recommends elaborating on the text of the document with regard to consistency and language (e.g., some cross-references have to be updated, and the text should be screened for the correct use of words, e.g. "pubs" was used in several instances when actually "pups" was meant).

3.1.1 Substance and volume of production

At room temperature, methenamine is a flammable organic amine that occurs as hygroscopic and colourless or white crystals, granules, or powder. It has a melting point > 270 °C and a low vapour pressure (0.0005 hPa at 20°C). Sublimation occurs at around 230 °C. The purity of methenamine is reported as 99-99.5% w/w with < 5% water as the only impurity. Commercial products may contain 1.5-4% paraffin oil and 0.5%-3% amorphous silica as additives. In the EU (of 25?) methenamine is produced by several companies with a total production of about 39,000 tons per year.

3.2 Specific comments

3.2.1 Exposure assessment

The main use (ca. 95%) of methenamine is as cross-linking agent in phenolic and urea-formaldehyde resins and in rubber. About 3% are used as chemical intermediate in nitration reactions. About 2% are used for the production of fuel tablets. Other uses are considered to be negligible.

Occupational exposure may occur mainly through the respiratory and the dermal routes with highest exposures occurring to dust during the handling of powdery substance or substance preparations in the manufacture and use of phenolic resins. For these scenarios, shift average inhalation values of 12 and 7.5 mg/m^3 were estimated based on "analogous data" and EASE calculations. The SCHER notes that the use of the "analogy scenario" (i.e., manual dumping of powder in a formulating company) should be justified

better, as the relevance of this scenario for the methenamine situation is not obvious from the current text in the RAR.

The by far highest dermal exposure was estimated to be 3000 mg/person/day during the manufacture and use of phenolic resins. Again, this estimate was based on "a analogy scenario" (the same as above). This approach should be justified in a more elaborated way for the reason given above.

Consumer exposure may occur through the use of methenamine in solid fuel tablets, e.g. for camping stoves. Methenamine is further used as auxiliary ingredient in limestone removers (e.g. for coffee machines) and in floor and carpet cleaners. Cosmetics may contain methenamine; if used as preservative in cosmetics the maximum authorised concentration is 0.15%. Methenamine may also be used as preservative (E239) in Provolone cheese.

Methenamine is used as treatment for urinary tract infections in humans.

3.2.2 Effect assessment

Methenamine is readily absorbed from the gastrointestinal tract and distributed widely into body fluids. 10 -20% of the ingested dose is hydrolysed to formaldehyde and urea prior to excretion in the kidney. The plasma half-life is about 4 hours and 80-90% are found in the urine within 24 hours after a single 1 g dose. Methenamine can pass the placenta barrier and is detectable in amniotic fluid and in human breast milk.

Methenamine is of low acute oral and dermal toxicity in animals (LD_{50} values greater than 20,000 mg/kg bw for the oral and greater than 2000 mg/kg bw for the dermal route with no specific signs of toxicity). In humans, inflammation of the bladder and an increased concentration of nitrogen in the blood have been reported following an inadvertent ingestion of a methenamine overdose.

Methenamine was only very slightly irritating to the skin and eyes of rabbits, but has caused dermatitis in humans.

Methenamine was a strong skin sensitizer in a guinea pig maximisation test which was performed according to Magnusson and Kligman. It has also caused skin sensitisation in humans. Cases of allergic rhinitis and asthma have been reported in occupational settings, where co-exposure to irritant and sensitising agents existed. Provocative testing with inhaled methenamine resulted in respiratory hyper-reactivity and indicated that methenamine has caused respiratory sensitisation in these subjects. More recently Merget et al (1999) investigated 17 exposed workers. Two former baggers showed skin sensitization reactions to methenamine by patch testing but there was no indication of an increased risk for occupational asthma at air concentrations in the range of 0.2 – 2.6 mg/m^3. It is the opinion of the SCHER, that the study by Merget et al., 1999 can be used to "de-classify" methenamine as possible respiratory sensitizer.

No adverse effects were noted in limited studies on mice and rats dosed with up to 2500 and 1500 mg/kg bw/day, respectively, in drinking water, feed or by gavage for 13 – 104 weeks. No systemic effects were noted in rabbits dosed dermally for 6 weeks with an aqueous methenamine solution at a concentration of 0.20%.

In patients receiving methenamine up to a dose level of 4000 mg/day for preventive long-term treatment of urinary tract infection no adverse effects were noted (equivalent to a NOAEL of 57 mg/kg bw/day for a 70 kg person). Larger doses of methenamine (8 g daily for 3 to 4 weeks) have caused bladder irritation, painful and frequent urination, albuminuria, and gross haematuria. The SCHER agrees that the NOAEL of 57 mg/kg bw/day is used later for the repeated dose risk characterisation process.

At high test concentrations, methenamine was mutagenic in bacteria and induced chromosomal aberrations *in vitro*. No genotoxic effects were found *in vivo* in a chromosomal aberration test and in a dominant lethal test.

No carcinogenicity studies that meet current standards were performed with methenamine. From a number of limited life-time studies on rats and mice, all using the oral route of exposure, there was no indication of a carcinogenic potential. With regard to the carcinogenicity of formaldehyde, which may be released from methenamine, the RAR states that "A valid cancer study with administration of formaldehyde via drinking water to rats did not demonstrate increased tumour 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". The study on which this statement is based is the carcinogenicity study performed by Til et al. (1989), the 2 year drinking water study of formaldehyde in rats (p. 83 of the RAR). The SCHER agrees with this conclusion.

Excess risks of skin, lung and bladder cancer were reported in workers exposed to methenamine in the steel and rubber industries. Because of simultaneous co-exposures to other chemicals, a clear association with methenamne exposure could however not be shown.

Only very limited data is available with regard to the reproductive and developmental toxicity of methenamine. Natvig et al. (1971) report that there was no influence on average litter size and body weights of F1 offspring of rats fed 100 mg methenamine/kg bw/day in a life-time study. Treatment associated effects on the postnatal development were shown in rats and Beagle dogs. A significant decrease in body weights was found in pups, which were born to dams treated during pregnancy and lactation with 2000 mg/kg bw/day and which were treated with the same dose for the first 20 weeks of life. Beagle dogs, fed about 31 mg kg had a slightly higher percentage of stillbirths, and the weight gain and survival to weaning was slightly impaired. 15 mg/kg bw were without adverse effect in this study.

In a surveillance study of Michigan Medicaid, 209 women received methenamine for urinary tract infection during the first trimester. The total incidence for both major and minor congenital birth defects was 3.8%, which is close to the expected level for spontaneous defects. This data does not support an association between methenamine and congenital defects. A controlled clinical trial with 206 pregnant women gave also no indication of an effect on pregnancy outcome by 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, respectively). The SCHER agrees that a NOAEL of 27 mg/kg bw/day is used for the developmental risk characterisation process.

3.2.3 Risk characterisation

The SCHER notes that the cross-reference to tables 4.1.1.2.6.A and 4.1.1.2.6.B in the risk characterisation chapter 4.1.3.2.1. ("Introductory remarks") has to be amended as such tables do not exist in the document.

The most critical effect of methenamine exposure is the potential for skin sensitisation. Concern were also identified for reproductive and developmental toxicity (because of the poor database on reproductive toxicity, a MOS approach was not performed). There were no concerns identified for irritation, mutagenicity and carcinogenicity.

Workers

Whilst the most relevant occupational exposure routes are the dermal and the respiratory routes, the available repeated dose toxicity data is limited to the oral route. For the oral route 100% absorption is assumed based on the available data, default values of 50% and 100% were chosen for the absorption by the dermal and respiratory routes of exposure, respectively, based on the physico-chemical properties of methenamine. SCHER finds the assumptions reasonable and agrees with the proposed default values.

The highest occupational exposure may occur during the handling of powdery substance or substance preparations (containing up to 15% methenamine) in the manufacture and the use of phenolic resins. For these scenarios, shift average inhalation values of 12 and

7.5 mg/m^3 were estimated based on "analogous data" and EASE calculations (see above). The highest dermal exposure was estimated to be 3000 mg/person/day during the manufacture and use of phenolic resins.

Comparing anticipated human internal doses for combined dermal and respiratory exposure (0.06 – 27 mg/kg bw/day depending on the exposure scenario) with the NOAELs reveales large Margins of Safety (MOS) for acute toxicity, and for all scenarios with regard to repeated dose toxicity except for the formulation of phenolic resin systems (scenario 2) with a MOS of only 2.5. With regard to developmental toxicity, concern after dermal exposure is reached for scenarios 2 (formulation of phenolic resin systems, MOS 1.2), 3 (production of fuel tablets, MOS 7.2), and 4 (production of formulations used in corrosion prevention and as photo chemicals, MOS 8.6). There are no concerns with regard to skin and eye irritation, mutagenicity, reproductive toxicity and carcinogenicity (all conclusions (ii)[1]. The SCHER agrees with these conclusions, and with conclusion (iii) for scenario 2 with regard to repeated dose toxicity, and for scenarios 2, 3, and 4 with regard to developmental toxicity.

The SCHER also agrees with the conclusion (iii) for all exposure scenarios because of the concerns for sensitisation as a consequence of dermal exposure during methenamine manufacture, and the manufacture of products or use of preparations containing methenamine.

The SCHER also agrees with conclusion (ii) for respiratory sensitisation.

Consumers:

In this chapter the dermal exposure through cosmetics is considered the most relevant consumer exposure and is calculated to amount to 0.445 mg/kg bw/day (i.e., 0.225 mg/kg bw systemic exposure), based on a use level of 0.15% methenamine in cosmetics. The SCHER has three comments: 1) in chapter 2.2 (use pattern), the use in cosmetics is excluded from further consideration. Chapter 2.2 should therefore be amended. 2) In chapter 4.1.1.2 it is stated, that reliable information on the concentration of methenamine in cosmetics is not available. Chapter 4.1.1.2 should therefore be amended. And, 3) the SCHER notes that methenamine may be used in cosmetics in higher concentrations if its main function is not that of a preservative. The text referring to the Cosmetics Directive on p. 107 should therefore be corrected (cf. also ongoing review of "Preservative substances used for other purposes in cosmetic products" by the EU Scientific Committee on Consumer Products).

Dermal exposure of consumers through other uses (limestone removers, floor and carpet/upholstery cleaners) and through the respiratory route is considered negligible.

Significant oral exposure may occur through the use of methenamine as medicinal product in the treatment of urinary tract infection, and through the consumption of provolone cheese (the latter calculated as 1.25 mg/day resulting in a systemic exposure of up to 0.021 mg/kg bw/day)

This results in large MOS values with regard to acute toxicity, repeated dose toxicity and reproductive toxicity effects. There were no concerns identified for irritation, mutagenicity and carcinogenicity. The SCHER therefore agrees with the conclusion (ii) for these endpoints.

[1] *According to the Technical Guidance Document on Risk Assessment – European Communities 2003:*

- *conclusion i): There is a need for further information and/or testing;*
- *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 iii): There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.*

Because of the strong skin sensitizing properties, there is a need for limiting the risks with regard to the dermal exposure to cosmetics and through the use in solid fuel tablets. The SCHER therefore agrees with conclusion (iii) for these scenarios. The SCHER also notes that the present text in RAR chapter 4.1.1.3 referring to the exposure through solid fuel tablets should be re-considered. As it stands now, it concludes on the basis of very limited data that this exposure "may be considered negligible".

Man exposed via the environment:

The indirect exposure of humans via environment, i.e. through food, drinking water and air was considered to be very low. The SCHER agrees with the conclusion (ii).

4. REFERENCES

IARC Monographs Vol. 88. Formaldehyde, 2-Butoxyethanol and 1-tert-Butoxypropan-2-ol. December 2006. 478 pages; ISBN 92 832 1288 6.

5. LIST OF ABBREVIATIONS

EASE	Estimation and Assessment of Substance Exposure Physic-chemical properties
LD_{50}	median Lethal Dose
MOS	Margin of Safety
NOEL	No Observed Effect level
RAR	Risk Assessment Report
TGD	Technical Guidance Document