FOREWORD INTRODUCTION

4,5-DIHYDROXY-1,3-BIS(HYDROXYMETHYL)IMIDAZOLIDIN-2-ONE
CAS N°: 1854-26-8

COVER PAGE

SIDS Initial Assessment Report
for
10th SIAM

(Tokyo, 15-17 March 2000)

Chemical Name: 4,5-Dihydroxy-1,3-bis(hydroxymethyl)imidazolidin-2-one

CAS No.: 1854-26-8

Sponsor Country: Germany

National SIDS Contact Point in Sponsor Country:

Mr. Jan Ahlers

HISTORY:

SIDS Dossier and Testing Plan were reviewed at a SIDS Review Meeting in 1993 where the following SIDS Testing Plan was agreed.

no testing ( )
testing (X)

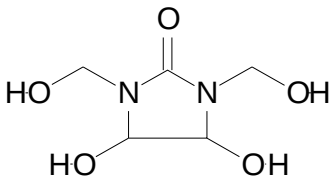
- Micronucleus test
- Developmental toxicity test

COMMENTS:

Deadline for circulation: 30 November 1999

Date of circulation: 30 November 1999
(To all National SIDS Contact Points and the OECD Secretariat)

SID INITIAL ASSESSMENT PROFILE

CAS No.	1854-26-8
Chemical Name	4,5-Dihydroxy-1,3-bis(hydroxymethyl)imidazolidin-2-one
Structural formula	

CONCLUSIONS AND RECOMMENDATIONS

The substance is currently of low priority for further work

SHORT SUMMARY WHICH SUPPORTS THE REASONS FOR THE CONCLUSIONS AND RECOMMENDATIONS

The production level of dimethylolglyoxalmonoureine (DMDHEU) in Germany was 10,000-15,000 t in 1991. The major part is produced at one site. The production volume at this site decreased continually during the last years to a capacity of 1,000-5,000 t/a. All the produced dimethylolglyoxalmonoureine was used in the textile industry to produce easy care fabrics by crosslinking the cellulose molecules.

Environment

Dimethylolglyoxalmonoureine has a log Kow of –2.2, a vapour pressure of 26 hPa and is miscible with water. Based on the physico-chemical properties of dimethylolglyoxalmonoureine the preferred compartment is the hydrosphere.

Dimethylolglyoxalmonoureine can be classified as inherently biodegradable. In a sewage treatment plant simulation test a mean DOC elimination of 27 % was found.

No bioaccumulation study is avaialble. The log Kow indicates no potential for bio- or geoaccumulation.

Short-term tests with fish, daphnids and algae and a long-term test with daphnids are available. The following effect values were found: *Leuciscus idus:* 96h-LC_{50} = 2200 mg/l; *Daphnia magna*: 48h-EC50 > 500 mg/l, 21d-NOEC = 100 mg/l; *Scenedesmus subspicatus*: 96h-EC_{50} = 28.4 mg/l, 96h-NOEC = 15 mg/l. However, in the tests the content of active substance was 40 % for the short-term tests and 70 % for the daphnia reproduction test. The most sensitive species was the green algae *Scenedsmus subspicatus*. A NOEC for the pure substance of 15 mg/l * 0.4 = 6 mg/l was found. With an assessment factor of 10 a $PNEC_{aqua}$ of 600 µg/l was derived from this value.

Human Health

DMDHEU has a very low acute toxicity and does not cause primary irritation.

With regard to the wide spread use, the incidence of contact dermatitis from specific textile-finishing resins is regarded to be very low. Products containing the substance and formaldehyde in concentrations of $\geq$ 0.2% may induce skin sensitization.

Repeated dose toxicity in rats and mice revealed also a very low toxic potential for oral application over 90 days with NOAELs of 3,000 mg/kg in rats and 6,000 mg/kg in mice .

No indication of toxic effects on reproductive function in subchronic studies in rats and mice nor embryotoxicity in rats was found (NOAEL > 640 mg/kg/day).

In bacterial tests, DMDHEU did not show mutagenicity. Whereas in Drosophila melanogaster a four-fold increase in the sex-linked recessive lethal events was found, there was no indication of induction of reciprocal translocation. In an *in vivo* micronucleus test the substance did not show clastogenicity. Therefore, there is no evidence for DMDHEU to possess a relevant mutagenic or clastogenic activity.

The chemical exhibits a very low toxic potential ,and no local or organ-specific effects were detected.

IF FURTHER WORK IS RECOMMENDED, SUMMARISE ITS NATURE

4,5-Dihydroxy-1,3-bis(hydroxymethyl)imidazolidin-2-one

CAS-NO.:1854-26-8			PROTOCOL	RESULTS
PHYSICAL CHEMICAL				
2.1	Melting Point		NA	-35 °C
2.2	Boiling Point		NA	106 °C (at1013 hPa)
2.3	Density		NA	1360 kg/m^3
2.4	Vapour Pressure		Calc.	26 hPa at20 °C
2.5	Partition Coefficient (Log Pow)		OECD 107	- 2.2
2.6 A	Water solubility		NA	miscible at 20°C
ENVIRONMENTAL FATE / BIODEGRADATION				
3.3	Transport and Distribution		Calculated	in air: 0 %
			(fugacity level 1 type)	In water 100 % in soil 0 % in sediment 0 %
3.5	Biodegradation		OECD 301A	not readily biodegradable
			OECD 303A	mean DOC elimination: 27 %

CAS-NO.:1854-26-8		SPECIES	PROTOCOL	RESULTS
ECOTOXICOLOGY				
4.1	acute/prolonged toxicity to fish	*Pimephales promelas*	DIN 38 412/15	LC_{50} (96 hr) = 2200 mg/l
4.2	acute/prolonged toxicity to aquatic invertebrates (daphnia)	*Daphnia magna*	84/449/EEC, C.2	EC_{50} (48 hr) > 500 mg/l
4.3	toxicity to aquatic plants e. g. algae	*Scenedesmus subspicatus*	UBA	EC_{50}(72 hr) = 36.9 mg/l EC_{20}(72 hr) = 22.9 mg/l
4.4	toxicity to microorganisms	*Pseudomonas putida*	DIN 38412/8	EC_{50}(17 hr) =2200 mg/l
4.5.2	chronic toxicity to aquatic invertebrates (daphnia)	*Daphnia magna*	XI/681/86 EEC	NOEC (21 d) =100 mg/l
TOXICOLOGY				
5.1.1	acute oral toxicity	rat	other	LD_{50} = >10,000 mg/kg LD_{50} = >2880 mg/kg
5.1.2	acute inhalation toxicity	rat	Inhalation Hazard Test (OECD 403, Annex) (at 20 and 150 °C)	Mortality at high temperature
5.2	Primary Irritation	rabbit	other (20 h)	no irritation
5.3	Sensitization	--	--	no data
5.4	repeated dose toxicity	rat	other: NTP (similar to OECD 408)	NOAEL(13 wk) = 3000 mg/(kg*d)
		mouse	other: NTP (similar to OECD 408)	NOAEL(13 wk) = 6000 mg/(kg*d)
5.5	genetic toxicity in vitro	S. typhimurium (TA100, 98, 1535, 1537) (preincubation)	NTP, acc. to OECD 471 (modified)	weakly pos. in TA100 with metabolic activation
		Ames test (TA102) (standard plate, preincubation)	acc. to OECD 471 (reduced, modified)	negative (with and without metabolic activation.)
	bacterial test (gen mutation)			+/- (with metabolic activation) +/- (without metabolic activation)
5.6	genetic toxicity in vivo	SLRL and RT (Reciprocal Translation) (Drosophila)	other: NTP (similar to OECD 471 (SLRL)	positive (SLRL), negative (RT)
		mouse: MN assay	OECD 474	negative
5.7	Carcinogenicity	--	--	no data

5.8	toxicity to reproduction	rat	other: NTP (similar to OECD 408)	no effect on sex organs: NOAEL(13 wk) = 3000 mg/(kg*d)
		mouse	other: NTP (similar to OECD 408)	no effect on sex organs: NOAEL(13 wk) = 6000 mg/(kg*d)
5.9	developmental toxicity / teratogenicity	rat	OECD 414	NOAEL = 1000 mg/(kg*d) for maternal and embryonic toxicity
5.11	experience with human exposure	human	patch-test	Case studies indicate formaldehyde to be the causative agent in patients with textile dermatitis.

SIDS Initial Assessment Report

1. Idendity

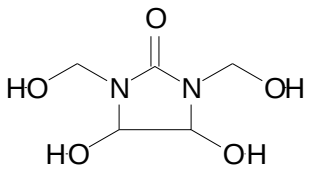
Name: 4,5-Dihydroxy-1,3-bis(hydroxymethyl)imidazolidin-2-one

Cas-No.: 1854-26-8

Synonyms: 1,3-Dimethylol-4,5-dihydroxyethyleneurea
Dimethylol-dihydroxy-ethylenharnstoff
Dimethylolglyoxalmonoureine
N,N'-Dimethylol-4,5-dihydroxyethyleneurea
Dimethylolglyoxalurea

Empirical formula: $C_5H_{10}N_2O_5$

Structural formula:



Two different products with different purities are produced by the German manufacturer: Fixapret CPN has a purity of about 45 % while Fixapret CP konz. has a purity of 75 %.

Impurities: Formaldehyde <1.5% w/w
Glyoxal (traces)
Urea (traces)
Sodium formiate (traces)

Additive: water 25% (Fixapret CP konz.) resp. 55 % (Fixapret CPN) w/w

In the further assessment all PECs and PNECs are related to a 100% pure substance.

2. General Information on Exposure

The production level of textile-crosslinking products worldwide was 150,000 t in 1991. 60 - 70% of these products are substances based on dimethylolglyoxalmonoureines (methyl- and other acetals included, the concentration of dimethylolglyoxalmonoureines in these products is 40 - 70%).

All the produced dimethylolglyoxalmonoureine was used in textile industry to produce easy care fabrics by crosslinking the cellulose molecules. The consumption volume of textile-cross-linking products in Western Europe was about 21,000 t in 1991.

The production level of dimethylolglyoxalmonoureine in Germany was 10,000-15,000 t in 1991. The major part is produced at one site. The production volume at these site decreased continually

during the last years to a capacity of 1,000-5,000 t/a. In 1998 the actual production volume was 2203 t/a. There is no information available about export or import volumes.

In Germany, the consumption volume of textile-crosslinking products (60 - 70% based on dimethylolglyoxalmonoureines) was about 5,500 t with decreasing tendency. Thus the consumption volume of dimethylolglyoxalmonoureine in Germany in 1991 was 5,500 t · 70% (40-70% in concentration) · 70% (chemistry based on dimethylolglyoxalurea) = 2,700 t in 1991.

The production volume of dimethylolglyoxalmonoureine in France is 1000 – 2000 t/a. The use pattern is the same as described above.

During production in Germany, an unknown amount of dimethylolglyoxalmonoureine is emitted into the waste water.

During processing in textile industry, releases are to be expected due to liquor residues. Furthermore, it is supposed that an unreacted fraction of the subtance remains on the textile which will be emitted during the next wash. Quantitative data about these releases are not available.

During production and processing, releases of formaldehyde are expected. Because of lack of data these releases cannot be considered by this assessment report.

3. Environment

3.1 Environmental Exposure

3.1.1 General Discussion

Dimethylolglyoxalmonoureine is miscible with water. Based on the molecular structure, a Henry's law constant of $1.04 \cdot 10^{-17}$ $Pa \cdot m^3 \cdot mol^{-1}$ is calculated according to the model of Hine & Mookerjee. This value indicates that the substance is not volatile from water solution. The values for boiling point and vapour pressure (26 hPa) cited in the SIDS seem to be related to the water additive.

Its estimated log Pow of -2.2 indicates that there is no considerable potential for bio- or geoaccumulation.

Based on the physico-chemical properties, the preferred environmental compartment of dimethylolglyoxalmonoureine is the hydrosphere.

In a DOC die away test according to OECD guideline 301A biodegradation of 65 % after 28 days and of 79 % after 49 days was achieved (BASF 1996a). From this test it can be concluded that the substance is inherently biodegradable. In addition, a simulation test according to OECD 303A was conducted over 85 days. (BASF 1996b). In this test a mean DOC elimination of 27 % was found. For the further exposure assessment this elimination rate is transferred to real sewage treatment plants.

There is no information available about hydrolysis or photolysis in water.

3.1.2 Predicted Environmental Concentration

a) Production

For the release of dimethylolglyoxalmonoureine during its production, we would consider the following scenario according to the EU Technical Guidance Document:

Based on a maximum production volume of 5,000 t/a and an emission rate of 0.3% during production, a total amount of 15 t/a is emitted into the waste water. With an elimination factor of 27% for treatment plants, 10.95 t/a are emitted into the river (10%-ile flow = 734 m^3/s) during 300 production days per year.

The predicted environmental concentration is

$$\mathbf{PEC} = \frac{10.95 \cdot 10^6 \text{ g/a}}{1.9 \cdot 10^{13} \text{ l/a}} = \mathbf{0.6\ \mu g/l}$$

b) Use in textile industry

Emissions occur during equipment cleaning and when liquor residues are discharged. The release fraction is assumed to be 1% of the processing amount (this factor is based on data from industry on the textile finishing procedure). Furthermore, it is assumed that a model site is processing 70 t/a (worst case, industrial data) during 270 days per year (Technical Guidance Document, table B 3.12).

⇒ emission into the sewage 1% · 70 t/a = 0.7 t/a
⇒ emission 2.6 kg/d
⇒waste water flow: 2000 m^3/d
⇒ $C_{influent}$ = 1.3 mg/l
⇒elimination 27%, dilution 1:10
⇒ **PEC = 95 µg/l**

It is not likely to assume *a priori* that the substance reacts completely with the cellulose fibres. A (probably small) fraction may remain on the textile, where it will be removed during the next wash. Neither quantitative data nor an appropriate emission model are available, therefore this emission path can not be assessed at this time. However, as these releases occur widely dispersed via household waste waters, the resulting environmental concentrations are expected to be negligible.

3.2 Effects on the Environment

3.2.1 Aquatic effects

Available data

The following ecotoxic effect concentrations, corresponding to the aquatic environment, are available:

a) fish
Leuciscus idus 96h-LC_{50} = 2200 mg/l (BASF 1990)
(content of active substance: 40 %)

b) invertebrates

Daphnia magna 48h-EC_{50} > 500 mg/l (BASF 1988a)
(effect: immobilisation; content of active substance: 40 %)

Daphnia magna: 21d-NOEC =100 mg/l (BASF 1998)
(effect: reproduction; content of active substance: 70 %)

c) algae

Scenedesmus subspicatus 72h-EC_{50} = 36.9 mg/l (BASF 1988b)
(endpoint: biomass; content of active substance: 40 %) 72h-EC_{20} = 22.9 mg/l
96h-EC_{50} = 28.4 mg/l
96h-EC_{20} = 19.2 mg/l

A NOEC of 15 mg/l after 72 h can be derived from the original test data.

d) bacteria

Pseudomonas putida 17h-EC_{50} = 2200 mg/l (BASF 1988c)
(effect: growth inhibition; content of active substance: 40 %)

Activated sludge 30min-NOEC = 1000 mg/l (BASF 1996c)
(effect: inhibition of respiration, content of active substance:74 %)

All values are nominal concentrations.

There is no information about possible effects caused by the formaldehyde impurity.

Determination of $PNEC_{aqua}$

The most sensitive species in short- and long-term tests was the green algae *Scenedesmus subspicatus*. A 72h-NOEC of 15 mg/l was found. However, in the test the content of active substance was 40 %. Therefore, for the pure substance a NOEC of 15 mg/l * 0.4 = **6 mg/l** is resulting. As long-term toxicity tests with species from 2 trophic levels are available, according to the TGD an assessment factor of 50 has to be used for the derivation of the PNECaqua. However, as algae are about 2 orders of magnitude more sensitive to dimethylolglyoxalmonoureine than fish as shown in the available short-term tests, the lowering of the assessment factor to 10 seems possible
PNECaqua = 6 mg/l / 10 **=600 µg/l**

3.2.2 Terrestrial organisms

There are no data available on terrestrial organisms.

3.3 Initial Assessment for the Environment

The PEC/PNEC ratios are calculated as follows:

	PEC [µg/l]	PEC/PNEC
production	0.6	0.001
textile finishing	95	0.16

4. Human Health

4.1 Human Exposure

4.1.1. Occupational Exposure

Workers can be exposed to DMDHEU during production, processing at production site and during use as cross-linking agent in the textile industry.
No data on occupational exposure to DMDHEU are available.

Although at production sites the synthesis of DMDHEU and its processing occurs in closed system, some activities like filling/emptying and maintenance can lead to an exposure to the substance.

An estimation of the exposure made using the model EASE (Estimation and Assessment of Substance Exposure; TGD, 1996), worst case assumptions and no use of personal protective equipment, results in exposure levels of up to 50 ppm for inhalation and up to 158 mg/d for dermal exposure.

The exposure to DMDHEU during processing in the textile industry is thought to be higher, with an estimated value up to 200 ppm for inhalation and up to 2100 mg/d for dermal exposure.

For DMDHEU no workplace exposure limit is established, whereas for Formaldehyde in Germany the MAK-value is 0.5 ppm (1999) and the PEL in USA is 0.75 ppm (OSHA, 1998).

4.1.2. Consumer Exposure

Although DMDHEU is not a consumer product, finished textiles containing small quantities of unreacted DMDHEU can be a potential source of exposure for the general population. During a proper textile finishing process more than 90% DMDHEU reacts with the fabrics.

It is estimated that currently about 10,000 t/y are used worldwide for textile finishing. This is about 10% of the total market of resins with decreasing tendency; in Europe the percentage is even lower. The total amount of 10,000 t is sufficient for finishing about 300,000 t textiles.

It has to be noted that a dermal exposure is possible only with new, unwashed clothes because the first laundry removes the unreacted DMDHEU totally.

A gross estimation of the dermal exposure, carried out with several worst case assumptions, results in a maximal dermal exposure of 0.5 g/d for the period of exposure.

Small amounts of formaldehyde are in the unreacted DMDHEU and in the reaction products in form of methylol groups on the finished fabric.

Some countries have set limits for the free formaldehyde (e.g. 75 ppm according to Öko-Tex standard 100).

This free formaldehyde decreases however significantly during storage (e.g. at relative moisture of 60% and 20 °C the values are halved).

Products containing formaldehyde in concentrations of $\geq$ 0.2% may induce skin sensitization (BASF, Technical Information, 1999).

4.1.3. Indirect Exposure via the environment

Considering the physical-chemical properties and the no potential for bio- and geoaccumulation, no direct exposure to DMDHEU via the environment or through food products is to be expected for the general population.

4.2 Effects on Human Health

4.2.1 Toxicokinetics and Metabolism

Toxicokinetic studies were performed with DMDHEU still containing chemical by-products from chemical synthesis which were presumably identical to the two isomers of 1-(mono)methylol-4,5-dihydroxyethylene urea (MMDHEU): ≥90 % DMDHEU, ≤10 % MMHEU). No attempts were made to isolate DMDHEU since no successful procedures were available (Jeffcoat, 1985).

After *intravenous* administration of ca. 50 mg/kg bw of ^{14}C-DMDHEU (prepared from ^{14}C urea) to male F-344 rats, excretion of ^{14}C was rapid and almost entirely via the urine (Jeffcoat, 1985): Within 6 h some 85 %, after 24 h ca. 95 %, and after 72 h about 96 % of the radioactivity was recovered in the urine; minor amounts were found in the feces, accounting for some 2.2 % in 24 h; less than 0.2 % was exhaled as $^{14}CO_2$ in 48 h.

Within 0.5 h, an average of 26 % of the dose was collected in the urinary bladder contents; tissues containing significant fractions of the dose after this period were the skin (13 %), muscle (12 %), blood (6 %), liver (6 %), and kidney (5 %). These levels were reduced by a factor of 4 to 12 after 2 h p.a. By 72 h p.a., less than 0.5% of the dose remained in the tissues, most of it in the muscle (0.3 %).

Urinary analysis (HLPC radiochromatogram) revealed that the profile of the excreted components correlated approximately with the composition of the test material (see above), indicating to negligible or no metabolism or degradation.

After *oral* application of ^{14}C-DMDHEU (by gavage) to rats, the percentage fraction absorbed from intestine, based on urinary excretion, was increased in relation to the dose for unexplained reasons [Jeffcoat, 1985]: 17 % at ca. 500 mg/kg bw, 28 % at ca. 1000 mg/kg bw, and 38 % at ca. 2000 mg/kg bw. The distribution pattern in the body was similar to that found after i.v. injection. More than 90 % of the radioactivity that was recovered in the urine was excreted within 24 h. After 72 h, residual quantities of radioactivity (<10 µg DMDHEU equivalents/g tissue, except higher amounts in intestine and cecum) were still left in the tissues and eliminated in delayed fashion, (comp. Jeffcoat, 1985: Tab. 7: tissue-blood ratios).

Dermal absorption in rats of [^{14}C]DMDHEU from a non-occluded dose site over a 144 h exposure period was ca. 5% of the applied dose for doses of 13 and 3.5 mg/cm² and ca. 1% of the applied dose for a dose of 0.3 mg/cm². Partial occlusion of the dose site resulted in a more than 4-fold increase in dermal absorption, probably due to increased hydration of the skin [Jeffcoat, 1985].

For the purpose of investigating dermal penetration from cotton-based fabrics, DMDHEU was prepared by two synthetic methods using ^{14}C-labelled formaldehyde [Robbins and Norred, 1984a,b]. New Zealand rabbits were treated for periods up to 48 h with fabric patches (10 x 12 cm) pretreated with defined quantities of the test material. Any interference with evaporations from the fabric was prevented by using a specially constructed housing chamber for the animals. Formaldehyde was studied in simultaneous groups for comparison.

The levels of radioactivity recovered from the skin were small, yet varied with the degree of occlusion of the patch, presence or absence of perspiration, type of DMDHEU synthesis, and the type of fabric. After *occlusive* treatment 1 to 1.4 %, after *semi-occlusive* bandage only 0.1 to 0.12 % of the applied dose was found, i.e. a factor of ca. 10 less than observed under stringent, i.e. occlusive conditions.

Perspiration in combination with occlusion, i.e. the most severe conditions increased skin incorporation by a factor of 1.8 (2.6% of the total dose contained in the patches). In muscle tissues underlying this skin, and in other tissues only insignificant levels of radioactivity (0.001 up to 0.005% of the acitivy in cloth) could be detected. This indicates that the material released from the treated textile is bound by skin and penetrates the dermis poorly, according to the authors. The highest amounts of exhaled CO_2 were below 0.02 %, but detectable.

In none of these penetration studies it could be clarified where the radioactivity in tissues resulted either from DMDHEU, Formaldehyde or other degradation products.

A further study was conducted in rhesus monkey,which is according to the investigator "..... the model more closely resampling human skin ...“ [Jeffcoat, 1984]. The application was performed with fabrics (96 cm²) treated with ^{14}C-DMDHEU (prepared from ^{14}C-formaldehyde) to monkeys over 48 hours at the skin of back either dry or with arteficial perspiration. Even though the level of radioactivity used was low, essentially all of the ^{14}C activity was found to remain on the textile fabric following the exposure to monkey's skin; the level of ^{14}C transferred from the fabric to the skin was at a level almost indistinguable from background. An average of 0.12 µCi of ^{14}C (equivalent to 0.029%) of the activity could be detected in or on the skin lying underneath the fabric. In expired CO_2, urine, feces, blood, muscle, adipose, liver, lung, kidneys, spleen, brain and testes no radioactivity (at or near background level) could be detected. Thus, no appreciable penetration from treated fabric could be demonstrated.

Conclusion: DMDHEU does not undergo noticeable metabolism or appreciable degradation. Furthermore, toxicokinetic and metabolic data suggest no evidence of bioaccumulation [Jeffcoat, 1985].

Experiments with finished textiles showed that formaldehyde or some breakdown product of DMDHEU could be released from the cloth treated with the textile finishing resin, but preferentially bound to the skin in small amounts and only poorly penetrated the epidermis, and that the absorption rate could be modified by surrounding conditions. In monkeys representing a more similar model of human skin no appreciable skin penetration could be demonstrated.

4.2.2 Acute Toxicity

Early studies suggest that DMDHEU is of low acute toxicity after oral and i.p. administration: The oral LD_{50} values were above 10,000 mg/kg bw (100% substance) in rat and mouse [IRDC, 1983a,b].

For a product containing 45 % DMDHEU in water (Fixapret CPN), the oral LD_{50} was >6400 µl/kg in rats, which corresponds to >2880 mg/kg bw (100% substance) [BASF, 1973]. There were no signs of toxicity.

In mice having received the same dose by i.p. injection, the only symptoms observed were dyspnea and atony. Macroscopic inspection showed no pathological findings [BASF, 1973].

At ambient temperature, the inhalation exposure for 8 h to an atmosphere highly enriched with vapors from a 45% aqueous solution (Fixapret CPN) caused no adverse effects in rats but some signs of dyspnea and irritation of mucous membranes [BASF, 1973]. However, vapors generated at 150 °C produced severe irritations and dyspnea and were lethal to rats within a few hours [BASF, 1973]. Spot-like hyperemia and edemas of the lung were prominent, while hydrothorax was seen in isolated cases. It is assumed that decomposition products arising at temperatures greater than 40 °C induced these serious effects.

Conclusion:
The available data show that DMDHEU has a very low acute toxicity.

4.2.3 Irritation

A 45% product of DMDHEU in water produced no signs of primary irritation following a 20-h exposure of the skin of rabbits; only marginal redness was observed directly after treatment [BASF, 1973]. Therefore, a severe skin irritating effect reported in another not assignable source [Marhold, 1972; cited in RTECS] could not be supported.

50 µl of this solution proved to be non-irritating to the eyes of rabbits [BASF, 1973]. According to Marhold (1972; cited in RTECS), a mild effect was seen.

Conclusion:
The data show that DMDHEU does not cause primary irritation.

4.2.4 Sensitization

DMDHEU has not been tested in animal studies for skin sensitization.

Human data
Thirty-seven substances which may be used in finishing textiles, incl. DMDHEU, were patch-tested in 66 patients, who, anamnestically and/or clinically, were suspected of suffering from a textile finish contact eczema. In 27 patients positive patch-test reactions to various textile finishes and additives were observed after 48-h contact. 8 out of 24 patients tested for DMDHEU have a positive response to DMDHEU (50% in aq.). 6 out of these 8 patients showed also a positive response to formaldehyde (5 % in aq.) [Malten, 1964].

Among 428 eczema patients patch-tested with textile finish resins from 1970 to 1980 15 had allergic textile dermatitis based on history, clinical features and patch test results. DMDHEU (10 % in petrolatum) induced a positive reaction only in three out of ten patients tested who also react to formaldehyde (2% in aq.). Test performed with the patch-test material revealed free formaldehyde in all samples (amount not specified) [Andersen and Harman, 1982].

25 patients with dermatitis suspected to be caused by permanently-pressed colored sheets were subject to further clinical investigations. One out of six patch-tested patients reacted to DMDHEU; none reacted to formaldehyde. Patch-test concentrations and further details were not given [Tegner, 1985].

Fregert and Tegner (1971) reported a case of dermatitis from non-iron sheets and pillow cases. The patch-test was positive to DMDHEU but negative to other textile finishing resins and to formaldehyde. Patch-test concentrations and further details were not given. This case is also reported in the review by Hatch and Maibach (1986).

10 out of 12 patients with positive patch-test reactions to older formaldehyde resins were patch-tested with formaldehyde (1 % in aq.) and DMDHEU (4.5 % in aq.). All ten subjects reacted to formaldehyde and DMDHEU. Whereas the formaldehyde content on the finished textile was measured, no analysis of formaldehyde content in DMDHEU used for patch testing was performed (Remark: According to the producer up to 1% of free formaldehyde is contained in DMDHEU. As a consequence of dilution additional formaldehyde is formed due to hydrolysis). In the 1960´s use of DMDHEU yielded fabrics with approximately 500 ppm free formaldehyde. Fabrics treated with the latest modified DMDHEU resins predictably contain less than 75 ppm free formaldehyde. Most clothing today yields free formaldehyde levels unlikely to cause contact allergy in formaldehyde-allergic individuals [Scheman et al., 1998].

Sommer et al., 1999 reported the case of a 10-year-old boy with eczema on both shins are wearing protective shin-pads. Patch-tested with a standard series and a textile series showed among others positive reactions to formaldehyde (++/++) and DMDHEU (+/+, 4.5 % in aq.). He did not react to the sample of his shin pads.

Conclusion:
The above mentioned papers do not allow to specify DMDHEU as the cause of contact eczema in patients with contact to resin treated textiles. Most cases showed positive patch-test reactions to formaldehyde and DMDHEU. Even in few cases reacting only DMDHEU it has to be considered that textile finishing resins on the basis of DMDHEU may contain up to 1% free formaldehyde. In none of the papers an analysis of the DMDHEU used for patch-testing was presented. Regarding a patch test concentration for DMDHEU of 5% and a free formaldehyde content of maximum 1% in DMDHEU 500 ppm formaldehyde in the test substance can be calculated; due to hydrolysis the actual formaldehyde concentration is higher. On the basis of the above reported cases the incidence of contact dermatitis from DMDHEU finished textile is regarded to be very low, especially compared to the wide spread use (about 300,000 finished textiles, see 4.1.2.).

According to EU regulations (EU, 1996) products containing formaldehyde in concentration of $\geq$ 0.2 % have to be classified as skin sensitizer.

4.2.5 Repeated-Dose Toxicity

In a 14-d repeated-dose toxicity study, male and female rats and mice (F-344 rats and B6C3F1 mice) were administered the test article by oral intubation at doses from 256 to 11,680 mg/kg bw/d (100% substance) (in total 12 treatments) [IRDC, 1983a,b]. No intoxication or toxicological significant macroscopic lesions or organ weight variations were evident in both species. Microscopically, no significant pathological events but the occurrence of a moderately inflammatory bilateral reaction in the nasal passages of the highest-dosed rats were found.

In two 90-d studies which were under the direction and support of the U.S. National Toxicology Program (NTP), groups of F-344 rats (10 male, 10 female each) and of B6C3F1 mice (10 male, 10 female each) received 1000, 3000 and 6000 mg DMDHEU (100%)/kg bw/d by gavage [IRDC, 1983a,b]. Reanalysis showed that the test solution contained 41.5 % of DMDHEU and 0.32 % of free formaldehyde [IRDC, 1983 b].

In the rats [IRDC, 1983a], mean body weight gain was retarded in the male top and median dose group, but not in females. No significant differences were seen at the 1000-mg dose level in both sexes. Yellow discoloration of the fur in the abdominal/ anogenital region and soft stool were prominent at the higher doses. One male in the high-dose group was noted for hypoactivity,

decreased grasping reflex, hypothermic extremities, and ataxia. Other clinical signs at various dose levels were considered incidental and unrelated to the test article.

No toxicologically significant organ weight changes occurred. At macroscopic post-mortem examination, no specific lesions were detected, but one high-dosed male having multiple yellowish linear macroscopic lesions in the right testis.

Histopathological inspection revealed no specific treatment-related organ lesions, except that two males of the 6000 mg/kg dosage level group suffered from mild mineralization in the heart, and one from moderate bilateral mineralization of the testes, both phenomena considered substance-related. No such damage was seen in the 3000-mg groups.

In mice, mean body weight gain was equal or significantly higher than the control. Microscopic examination of the tissues from mice of the control and 6000 mg/kg groups gave no indication to treatment-related morphological changes. Chronic interstitial pneumonia was not influenced or induced by DMDHEU because in both the control and the high-dose group this disease was correlated with serum positivity of the Sendai virus [IRDC, 1983b].

Conclusions:
Available experimental data are based on reliable studies conducted within the scope of the toxicological program under the auspices of U.S. NTP. The results clearly confirm the low toxicity already noted under single-dose conditions. The subchronic NOAEL for oral application was 3000 mg/kg in rat and 6000 mg/kg in mice (as 100% substance each).

4.2.6 Genetic Toxicity

4.2.6.1 Genetic Toxicity in vitro

In the Ames test (preincubation modification), DMDHEU showed weakly mutagenic activity in the tester strain Salmonella TA 100, beginning at high concentration of ca. 3 mg/plate only in the presence of metabolic activation (microsomal fraction derived from induced rat as well as from hamster liver), while the other strains used (TA98, TA 1535, and TA 1537) were non-responsive up to 10 mg/plate, the highest dose tested. No activity was seen up to 1 mg/plate. At higher doses, an increase in reverse mutations did not appear unless water served as solvent, whereas when DMSO was used for dilution, the test result was negative rather than positive (just a trend) [Zeiger et al., 1987]. It is unclear why the test conducted with DMSO was negative in contrast to that with water since the test product itself (41.4 % DMDHEU in water) and the test medium contains appreciable amounts of water.

In a further bacterial reverse mutation assay using the non-standard tester strain Salmonella TA102 (detection of base-pair substitutions), no mutagenic activity exerted by DMDHEU (75 % in water) could be discerned under the conditions applied [CCR, 1992]: The test was carried out as standard plate incorporation and preincubation assay in the presence and absence of a rat-liver microsomal activation system at concentrations of up to 10 mg/plate.

One rational for the application of the uncommon strain TA102 was its proven sensitivity to formaldehyde which is supposed to be the causative agent when released from DMDHEU.

4.2.6.2 Genetic Toxicity in vivo

Within the scope of the NTP genotoxicity program, DMDHEU was tested in Drosophila melanogaster SLRL (Sex-Linked Recessive Lethal) and RT (Reciprocal Translocation) assays using a very high concentration of 60 and 50 g/kg test medium, resp., (probably 100% substance) (≥0.28 M) either for 3-d feeding exposure of or for direct injection into adult male flies [Foureman et al., 1994].

A result was considered positive if the mutant frequency exceeded 0.15 % (at $p < 0.05$) or 0.1 % (at $p<0.01$).

An about fourfold increase in the sex-linked recessive lethal events was found for both application routes as compared with the untreated controls. But there was no significant effect for the induction of reciprocal translocations.

In a micronucleus assay, male and female NMRI mice received single oral doses of DMDHEU by gavage (500, 1000, and 2000 mg/kg bw as 75% solution containing 1 % of formaldehyde) [BIOPHARM, 1995]. Groups receiving either 20 or 80 mg/kg of cyclophosphamide served as positive controls. Routine sampling of bone marrow was at 24 h p.a., but for the top dose, time intervals of 24 h and 48 h were applied. Dose-range finding showed that all doses were well tolerated by the animals. Therefore, testing was carried out up to the limit dose of 2000 mg/kg bw.

Based on the ratio of the polychromatic to the normochromatic red blood cells, no indication to cytotoxic effects was found at any dose level. Analysis of the polychromatic erythrocytes gave no evidence of the induction of increased frequency of micronuclei.

Conclusion:
There is no evidence for DMDHEU to possess a relevant mutagenic or clastogenic potential. The data base is sufficiently reliable.

4.2.7 Carcinogenicity

There is no experimental data available.

Carcinogenesis bioassays were once announced to be performed in rats and mice under the direction of NTP (see subchronic studies by IRDC, 1983a,b, cover pages). However, obviously, their performance has been deferred according to an IARC notice (IARC, 1988). The reason for that decision cannot be concluded from the information available.

Conclusion:
On the basis of experimental data now available, there are no scientific grounds to assume that DMDHEU will harbor a carcinogenic potential.

4.2.8 Reproduction / Developmental Toxicity

There are no specific experimental studies concerning fertility. But within the scope of a comprehensive subchronic investigation in rats and mice, microscopic inspection of sex organs (testis, epididymis, prostate, preputial gland/uterus, ovaries, clitoral gland) gave no indication to morphological abnormalities [IRDC 1983a,b]. No histopathological changes were found up to 3000 mg/kg bw/d in male rats and up to 6000 mg/kg bw/d (100% substance) in both genders of mice and female rats.

In a guideline study, pregnant Wistar rats were treated by gavage with 250, 500, and 1000 mg/kg bw/d of DMDHEU (64.1 % in water, equivalent to 160, 320, and 640 mg/kg bw/d as 100% substance) from day 7 through 17 p.c. [HMR, 1998]. The highest dose was considered the recommended limit dose of the product.

No clinical signs of toxicity and no deaths occurred among the dams. Body weight development and food consumption was not influenced by the substance. Macroscopically, no substance-related effects were observed at necropsy, and histopathological examination gave no evidence of a significant increase in malformations.

Conclusion:
There is sufficient information from subchronic studies to conclude that DMDHEU is very unlikely to impair reproductive capacity in both sexes.

DMDHEU was neither maternally nor embryotoxic in rats under test conditions. There were no signs of toxicity in prenatal development of fetuses. The NOAEL is $\geq$ 640 mg/kg bw/d.

The NOAEL for reproduction and developmental toxicity is thus considered to be $\geq$ 640 mg/kg bw/d (100 % substance).

4.2.9 Other Human Health Related Information Available

No other toxicologically relevant information concerning human health could be located in the literature.

4.3 Initial Assessment for Human Health

4.3.1 Summary of experimental results/NOAEL

DMDHEU has a very low toxic potential following oral and dermal exposure in rats and mice: no local or organ-specific adverse effects have been detected. Inhalation studies with aerosolic DMDHEU are not available. However, the toxicity profile clearly suggests that no unexpected adverse effects should emerge from inhalation exposure.

Because of the lack of toxicity, all experimental NOAELs are upper doses of 640 mg/kg bw/d or higher (as 100% substance).

Data gaps for key endpoints of concern (genotoxicity, teratogenicity) have recently been covered by conducting guideline studies. The results substantiated the non-hazardous properties of DMDHEU.

4.3.2 Risk from Occupational Exposure

Most work-place scenarios correspond to short-term exposure situations. The lowest NOAEL of 640 mg/kg bw/d which represents the highest experimental dose in the testing of developmental toxicity (see 4.2.8) is the toxicological basis for risk assessment, though the subchronic NOAEL in rodents is $\geq$ 3000 mg/kg bw/d (see 4.2.5). Furthermore the very low dermal absorption rate has to be considered (see 4.2.1).

For *oral* ingestion, 20 % is adopted as reasonable intestinal absorption rate approximately found in rats after 24 h (see 4.2.1: Toxicokinetics). For this reason, the internal non-effective dose is 0.2 x NOAEL = 640 x 0.2 mg/kg bw/d = 128 mg/kg bw/d.

For *dermal exposure of DMDHEU itself*, an absorption rate of 1 % is assumed, which represents the upper experimental uptake through the skin of rats on semi-occlusive test conditions for 144 h (see 4.2.1: Toxicokinetics).

For *dermal exposure via finished textiles* it is prudent to use an absorption rate of 0.5% taking into account the results of the monkey study where no appreciable penetration could be demonstrated and of the rabbit kinetic study (see 4.2.1).

For *inhalation*, potential exposure to *aerosols* is assumed since aqueous solutions of DMDHEU are handled on site. 80 % thereof is thought to be inhalable, containing no significant respirable fraction and, therefore, being totally deposited in the upper and lower airways.

The comparison of toxicological with exposure data based on upper "worst-case assumptions" results in margins of safety (MOS) of distinctly greater than 100, generally, above 1000, except for one scenario in textile finishing where continuous inhalation exposure was assumed. In the latter case, the calculative "worst case" MOS resulted in a ratio slightly below 100.

Consequently, no situation at the work-place could be identified to give rise to concern over unreasonable risks arising from any route of potential exposure to DMDHEU.

4.3.3 Risk for Consumers

Finished textiles may be a potential source of exposure to DMDHEU.

Considering a calculated MOS of > 3300, the very low dermal absorption rate, the short period of the skin exposure to the product itself and the fact that not all the treated fabric is in direct contact with the skin, it can be concluded that no risk due to dermal exposure to DMDHEU for consumers is to be expected.

With respect to the formaldehyde issue, the published case studies do not allow to specify DMDHEU as the cause of contact eczema in patients with contact to resin-treated textiles. The incidence of contact dermatitis from specific textile finishing resins is regarded to be very low, especially compared to the wide-spread use. Products containing formaldehyde in concentration of $\geq$ 0.2 % may induce skin sensitization.

4.3.4 Risk for Man Indirectly Exposed via the Environment

In relation to the very low occupational risk (see 4.3.2), those risks via environmental sources like drinking water, air, and food are expected to be negligible.

5. Conclusions and Recommendations

5.1 Conclusions

Environemnt:
The results show that during production of dimethylolglyoxalmonoureine and textile finishing, a risk for the environment is not to be expected.

Human Health:

The chemical exhibits a very low toxic potential, and no local or organ-specific effects were detected. The risk for occupational exposure also under worst case conditions, for consumers and the risk via environment is also very low. Therefore it is concluded that DMDHEU is of no concern with respect to human health.

5.2 Recommendations

There is no need for further work.

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