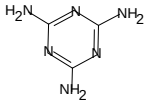
FOREWORD INTRODUCTION

MELAMINE

CAS N°:108-78-1

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	108-78-1
CHEMICAL NAME	**Melamine,** 1,3,5-Triazine-2,4,6-triamine
STRUCTURAL FORMULA	

CONCLUSIONS AND RECOMMENDATIONS

Environment:

The toxicity of the chemical to aquatic organisms is low. PEC/PNEC ratios are below 1 when based on realistic worst case conditions and on monitored concentrations. Therefore, melamine is currently considered of low potential risk and low priority for further work.

Health:

The toxicity of melamine is low. Repeated exposure resulted in urinary bladder stones and other lesions of the urinary tract. Bladder tumours occured only in male rats after prolonged irritation of the epithelium by the bladder stones. Melamine is not genotoxic. The exposure of workers and consumers is low. Therefore, melamine is currently considered of low potential risk and low priority for further work.

SHORT SUMMARY WHICH SUPPORTS THE REASON FOR THE CONCLUSIONS AND RECOMMENDATIONS

Melamine is produced in large amounts on few sites. Its main use is as an intermediate in the synthesis of melamine resins.

Environment:

The outstanding physical-chemical property concerning the risk assessment is a low n-octanol/water partition coefficient. Melamine is not readily biodegradable but adapted waste- water treatment plants can degrade it effectively. Water is the most relevant compartment in the environmental fate of the substance.

The ecotoxicity is low, data are available from different species and different trophic levels.

The environmental exposure estimations were based on some monitored concentrations and on the EUSES model. No relevant risk was detected for the environment. Most of the estimated risk characterisation ratios (PEC/PNEC) were lower than 1. Those few modelled risk characterisation ratios being slightly above 1 could be revised (and lowered to < 1) by assuming realistic worst case conditions.

Health:

The toxicity to mammals is also low. Studies ranging from skin irritation to carcinogenicity are available. Melamine is not genotoxic but it causes carcinomas of the urinary bladder at high doses in male rats only. Formation of bladder stones occurred and these calculi are necessary for the induction of tumours. Carcinomas are induced by continuous irritation of the bladder epithelium by the calculi, so that melamine acts only indirectly as a non-genotoxic carcinogen. A threshold concept can be used. Melamine is not irritating to skin and eye, not sensitising and not teratogenic.

No relevant risk was detected for humans. The estimated margin of safety for workers is at least 210, that for consumers at least 6000.

IF FURTHER WORK IS RECOMMENDED, SUMMARISE ITS NATURE

FULL SIDS SUMMARY

CAS NO: 108-78-1		SPECIES	PROTOCOL	RESULTS
PHYSICAL-CHEMICAL				
2.1	Melting Point			Ca. 350 °C
2.2	Boiling Point			Melamine decomposes at > ca. 280 °C.
2.3	Density			1574 kg/m^3
2.4	Vapour Pressure			4.7 x 10^{-8} Pa at 20 °C
2.5	Partition Coefficient (log Pow)		OECD107	-1.14
2.6	Water Solubility			3.1 g/l at 20 °C
	pH			Ca. 8 at 20 °C
	pKa			No data
2.9	Flammability			Non flammable
2.10	Explosivity			Not explosive
2.12	Oxidation Reduction Potential			No data
ENVIRONMENTAL FATE AND PATHWAY				
3.1.1	Photodegradation			No data
3.1.2	Stability in Water			No data
3.2	Monitoring Data			In air no data In surface water ≤ 0.0076 mg/kg In soil/sediment ≤ 0.32 mg/kg In biota ≤ 0.55 mg/kg
3.3	Transport and Distribution		Calculated (Fugacity Level 1 type)	To Air <0.000 001 % To Water 99.99 % To Sediment 0.000 1 % To Soil 0.006 % To Biota <0.000 001 %
3.4	Mode of Degradation in Actual Use		Waste water treatment plant	80-90 % degradation. Complete degradation by adapted microorganisms.
3.5	Biodegradation	activated sludge; Pseudomonas sp.	OECD302B, MITI, BOD.	Not readily biodegradable.
3.7	Bioaccumulation	Cyprinus caprio	OECD305C	BCF < 0.38.

FULL SIDS SUMMARY, cont. 1

ECOTOXICOLOGY				
4.1	Acute/Prolonged Toxicity to Fish	Leuciscus idus melanotus	DIN 38412/L20	$LC_{50,48h}$ > 500 mg/l
		Oryzias latipes	Modified MITI test II	$LC_{50,48h}$ = 1000 mg/l
		Poecilia reticulata		$LC_{50,96h}$ > 3000 mg/l
		Poecilia reticulata		$LC_{10,96h}$ > 4400 mg/l
4.2	Acute Toxicity to Aquatic Invertebrates *Daphnia*	Daphnia magna		$EC_{50,48h}$ > 2000 mg/l
4.3	Toxicity to Aquatic Plants e.g. Algae	Scenedesmus pannonicus		$EC_{50,4d}$ = 940 mg/l $NOEC_{4d}$ = 320 mg/l
4.4	Toxicity to Microorganisms	Activated sludge	OECD209	EC_0 > 1992 mg/l
4.5.1	Chronic Toxicity to Fish	Jordanella floridae	Early life stage toxicity	NOEC > 1000 mg/l
		Salmo gairdneri	Early life stage toxicity	$NOEC_{macroscop.}$ = 500 mg/l $NOEC_{microscop.}$ < 125 mg/l
4.5.2	Chronic Toxicity to Aquatic Invertebrates (*Daphnia*)	Daphnia magna		$NOEC_{21d,reprotox.}$ ≥ 32 mg/l $LC_{50,21d}$ > 32 mg/l $NOEC_{21d,tox.}$ = 18 mg/l
4.6.1	Toxicity to Soil Dwelling Organisms			No data.
4.6.2	Toxicity to Terrestrial Plants	Hordeum vulgare, Tritium aestivum, Raphanus sativus, Lepidum sativum, Pisum sativum		$EC_{50,4d}$ = 530mg/kg $EC_{50,4d}$ = 900mg/kg $EC_{50,4d}$ = 930mg/kg $EC_{50,4d}$ = 1100mg/kg $EC_{50,14d}$ = 1680mg/kg
4.6.3	Toxicity to Other Non-Mammalian Terrestrial Species (Including Birds)			No data.
TOXICOLOGY				
5.1.1	Acute Oral Toxicity	F344 rat	NTP	LD_{50} = 3161 mg/kg
		B6C3F1 mice	NTP	LD_{50} = 3296 mg/kg
5.1.2	Acute Inhalation Toxicity	rat		LC_{50} = 3248 mg/m^3
5.1.3	Acute Dermal Toxicity	rabbit		LD_{50} > 1000 mg/kg
5.2.1	Skin Irritation	rabbit; guinea pig		not irritating
5.2.2	Eye Irritation	rabbit		not irritating
5.3	Sensitization	human; guinea pig		not sensitizing

FULL SIDS SUMMARY, cont. 2

TOXICOLOGY, cont. 1				
5.4	Repeated Dose Toxicity	rat	14 d, oral with feed, NTP	NOEL = ca. 417 mg/kg bw
		rat	28 d, oral with feed, investigation of stone formation	NOEL = ca. 240 mg/kg bw
		rat	13 w, oral with feed, NTP	NOEL ≤ ca. 63 mg/kg bw
		mice	13 w, oral with feed, NTP	NOEL = ca. 1600 mg/kg bw
5.5	Genetic Toxicity In Vitro			*Results with / without metabolic activation*:
A.	Bacterial Test (Gene mutation)	Salmonella	6 different Ames tests	each: negative / negative
		Photobacterium phosphoreum	Bioluminescence assay	negative
	Bacterial Test (DNA damage)	E. coli	DNA damage and repair	negative / negative
		E. coli WP2s	Microscreen assay. Lambda prophage induction	positive / positive
B.	Non-Bacterial in vitro Test (Gene mutation)	Saccharomyces cerevisiae D4		negative / negative
		CHO cells	HGPRT forward mutation assay	negative / negative
		mouse lymphoma cells	forward mutation assay	negative / negative
	Non-Bacterial in vitro Test (Chromosomal aberrations)	CHO cells	Cytogenetics	negative / negative
		CHO cells	SCE assay	negative / equivocal
		CHO cells	SCE assay	negative / negative
	Non-Bacterial in vitro Test (DNA damage)	rat hepatocytes	UDS	negative
		rat hepatocytes	DNA-repair test	negative
		HeLa S3 cells	DNA synthesis inhibition test	negative
	Non-Bacterial in vitro Test (cell transformation)	Balb/c 3T3	Cell transformation assay	negative / negative
5.6	Genetic Toxicity In Vivo	mouse		
			2 different micronucleus assays	each: negative
		Drosophila	SLRL test	negative

FULL SIDS SUMMARY, cont. 3

TOXICOLOGY, cont. 2				
5.7	Carcinogenicity	rat	105 weeks, 2250 and 4500 ppm (males) or 4500 and 9000 ppm (females) with feed, NTP	positive in males, negative in females. NOEL = ca. 126 mg/kg bw.d
		rat	24-30 months,100 to 1000 ppm (males) or 100 to 2000 ppm (females) with feed	negative in males, negative in females
		mouse	2 years, 1000 and 10000 ppm with feed, NTP	negative in males, negative in females.
		rat, males	36 weeks, 3000 to 30000 ppm with feed	positive
		mouse	initiation-promotion experiment	Melamine is not an initiator
5.8	Toxicity to Reproduction			No special data
5.9	Developmental Toxicity/ Teratogenicity	rat	OECD 414	NOEL = ca. 400 mg/kg bw (maternal toxicity) NOEL = ca. 1060 mg/kg bw (foetal toxicity) Not teratogenic.
5.10	Toxicokinetics	rat		Melamine is not metabolized and is fast eliminated with urine.
5.11	Experience with Human Exposure			Workplace concentrations of 0.1 to 1.14 mg/m^3 were monitored in processing plants.

SIDS Initial Assessment Report
for the
8th SIAM
(Paris, 28 - 30 October 1998)

Chemical Name: **Melamine**
(1,3,5-Triazine-2,4,6-triamine)

CAS No: 108-78-1

Sponsor Country: Austria

National SIDS Contact Point in Sponsor Country: MR Mag. Heinrich Kohlmann

HISTORY:

SIDS Dossier and Testing Plan were reviewed at the SIDS Review Meeting on 23 September 1993, where the following SIDS Testing Plan was agreed:

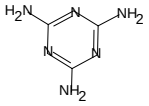
no testing ( )
testing (x): Developmental toxicity / teratogenicity study.

COMMENTS:

Conclusions and recommendations of the SIDS Initial Assessment Report on melamine were accepted at the 8th SIAM. Comments obtained in front of and at the meeting were incorporated in this revision of the SIAR. The comments were of minor importance for the overall evaluation so that it was accepted at the SIAM that the SIAR on melamine has not to be re-evaluated at a future SIAM.

1. IDENTITY

1.1 Identification

CAS number	108-78-1
Name	1,3,5-Triazine-2,4,6-triamine
Synonyms (some)	1,3,5-Triazine-2,4,6(1H,3H,5H)-triimine 2,4,6-Triamino-s-triazine Cyanuric Triamide Cyanurotriamine Isomelamine Melamine s-Triaminotriazine s-Triazine, 4,6-diamino-1,2-dihydro-2-imino-
EINECS-Number	203-615-4
Structural Formula	
Molecular Formula	$C_3N_6H_6$
Molecular Weight	126.13

1.2 Characterisation

Type of substance	organic
Physical state	solid (at 20 °C and 101 300 Pa)
Purity	> 99.8 % w/w
Additives	no additives

1.3 Physical-Chemical Properties

Melting point	ca. 350 °C. Decomposition and sublimation occurs at > ca. 280 °C.
Density 1 574 kg/m^3	at 20 °C.
Vapour pressure	4.7 x 10^{-8} Pa at 20 °C.
log Pow	-1.14 at 25 °C
Water solubility	3.1 g/l at 20 °C
pH ca. 8	at 3 g/l and 20 °C
Ion formation	Melamine is a weak base. It is neutral in the pH range 6 to 13. The cation $C_3N_3H^+(NH_2)_3$ is present in the pH range 1 to 4.
Ignition temperature	> 600 °C
Flammability	non flammable
Explosivity	not explosive
Oxidizing properties	no oxidizing properties

1.4 Classification

No classification is needed according to EC-Directives.

2. GENERAL INFORMATION ON EXPOSURE

2.1 Production Volume

Ca. 600 000 t/a are produced worldwide by ca. 30 producers. Ca. 250 000 t/a are used in Europe.

2.2 Uses and Functions

The main use (ca. 97 % in Europe, > 99 % in Germany) of melamine is the production of melamine resins, typically by reaction with formaldehyde (4).

Melamine resins or other melamine compounds are used in laminates (e.g. for tabletops), glues, adhesives, molding compounds, coatings, paper (to obtain wet strength), textiles (to obtain shrink resistance, water repellence, stain repellence, fire retardance), flame retardants or superplastisizer for concrete.

Melamine itself is used as a flame retardant in polyurethan foams in UK (7 000 t/a, i.e. 2.8 % of the European market) and possibly for some other minor applications (1 000 t/a, i.e. 0.4 % of the European market) as e.g. in paints for fire protection. Other earlier reported uses are probably of no importance nowadays.

The main user of melamine is therefore the chemical industry. Consumer may come into contact with melamine itself only in products where melamine is included in a polymer matrix.

2.3 Form of Marketed Products

Melamine is shipped as such to the processing facilities.

2.4 Sources of Release to the Environment

DSM Melamine, Netherlands, reports a release to waste water of 0.4 kg nitrogen per t of melamine produced and of < 0.02 kg nitrogen per t to the receiving river after the waste water treatment plant (WWTP).

Agrolinz Melamin, Austria releases ca. 300 t melamine per year with the waste water. The production capacity is ca. 50 000 t/a. The emission to air leaving the same production plant is 41 kg melamine per year.

Discharge into atmosphere during manufacturing and further processing of the melamine produced in West Germany in 1989 is estimated at 850 kg, and into waste water treatment plant of BASF AG, at 6 to 7 t. The contaminated residue (50 to 60 t/a) from production is landfilled as hazardous waste.

2.5 Information on Safe Handling Procedures

No special safety precautions are necessary when handling melamine. Protection against dust and use of goggles are recommended.

3. ENVIRONMENT

3.1 Environmental Exposure

The EUSES Programme for the Evaluation of Substances, Version 1.00, 1997 was used for the estimation of some exposures and as an aid in the risk evaluation. A compact report with input and output data is attached as an Annex. In most cases the default data of the programme were used. The degradation of melamine in the WWTP (80 to 90 %) was not taken into account as EUSES needs a rate constant as input for degradation. A rate constant is not available, only the overall degradation.

"Use pattern 1" of the EUSES programme contains the production of melamine and the processing to melamine resins and other melamine compounds. "Use pattern 2" is the application of melamine as a flame retardant in polymers and "use pattern 3" that in fire protective paints.

3.1.1 General Discussion

Based on the physico-chemical properties, water is the preferred environmental compartment of melamine. According to the generic FUGMOD model, version 1.0, OECD 1992 the following environmental distribution is estimated:

to air	< 0.000 1	%
to water	99.99	%
to soil	0.006	%
to sediment	0.000 1	%

Elimination from the water compartment:
Melamine can not be classified as readily biodegradable. Degradations of 0 % respectively 16 % were obtained in two Zahn-Wellens tests on inherent biodegradability. 80-90 % of melamine is eliminated by the WWTP of a producer. Complete elimination of melamine is found 8 hours after incubation with the activated sludge of the WWTP of another producer whereas no degradation occurred with the activated sludge of a domestic WWTP. It is concluded that microorganisms of WWTPs can adapt to melamine when continuously exposed.

Elimination from soil and sediment:
Melamine is slowly degraded in soil with a half life of 2-3 years.
Nitrification in soil was determined; up to about 18 % of the melamine-N nitrificates in 6-24 weeks.
The adsorption to soil is estimated to be low.

Elimination from air:
Apart from sedimentation of the melamine dust the only relevant information is the maximum of absorbance of melamine at 235 nm.

Distribution in a WWTP:
According to the EUSES model, without taking into account the monitored degradation within the WWTP, the following distribution was obtained:

fraction of emission	directed to:
$3x10^{-11}$	air
1	water
0.000 02	sludge

The majority of melamine stays within the water compartment, only minor parts are emitted to sludge.

No bioaccumulation of melamine is expected as a bioconcentration factor of < 0.38 was determined in fish (2).

3.1.2 Predicted Environmental Concentration (PEC) in water

A. PEC in the water at the local level

Data on emission to the waste water are available only for the production of melamine. It is assumed that a similar situation applies for the processing of melamine which is also performed in industrial chemical plants.

The following input parameters are used for a site specific estimation:
Release of melamine from production: 300 t melamine per year (Agrolinz Melamin).
80 % elimination in the WWTP.
Duration of emission: 300 days.
The lowest flow rate of the receiving river Danube is 63 x 10^6 m^3 / d.

$$PEC_{site\ specific,water} = 0.003 \text{ mg/l.}$$

EUSES modelled concentrations in the effluent of the WWTP are: 94 mg/l for production, 3.0 mg/l for processing to resins, 3.3 - 19 mg/l for formulations of polymers or paints. With a default dilution of 10 by the receiving river, which is rather low, $PECs_{local,water}$ = 0.30 - 9.4 mg/l are obtained.

B. PECs in the water at the regional level

The EUSES programme was used:

$$PEC_{regional,water} = 0.0042 \text{ mg/l}$$

C. Monitored concentrations

Japan monitored the concentration of melamine in rivers during 1986 to 1994 (12), (13) and (14). Concentrations in water ranged from below the detection limit of 0.0001 to 0.0076 mg/kg. No individual data are available, therefore no further correlations or evaluations of the monitored concentrations can be drawn.

Considering that the highest values were found only in a few of the 50 areas investigated these highest value may represent local PECs more likely than regional PECs.

D. Conclusion

For $PEC_{local,water}$ 3 data are available and are compared:

"P"$EC_{local,water,monitored}$ ≤ 0.0076mg/l
$PEC_{site\ specific,water}$ = 0.003 mg/l
$PEC_{local,water,modelled}$ = 0.3 - 9.4 mg/l

The modelled PEC is by orders of magnitude higher than the site specific PEC and also the monitored concentrations. The reasons are found in the actual degradation of melamine in WWTPs of the chemical industry (which is not used in the actual EUSES calculation) and in the higher dilution factors by the actual rivers at the production sites compared to that used by EUSES. The 2 parameters contribute to a lowering of the PEC by at least a factor of 100.

A **$PEC_{local,water}$ = 0.1 mg/l** is therefore estimated as an average of the 3 available results of different sources and is considered to be on the safe side when compared with the more realistic site specific and monitored concentrations.

3.1.3 PECs in compartments other than water

Local PECs:

Examples of outputs from the EUSES programme are:

$PEC_{local,air}$	< 0.000 001	to	0.000 2	mg/m^3
$PEC_{local,sediment}$	= 0.2	to	7	mg/kgwwt
$PEC_{local,agric.soil}$	= 0.000 2	to	0.006	mg/kgwwt
$PEC_{local,pore\ water\ in\ agric.soil}$	= 0.000 8	to	0.02	mg/l
$PEC_{local,natural\ soil}$	= 0.000 02	to	0.000 6	mg/kgwwt
Conc. in fish, local	= 0.36	to	10.9	mg/kg

Concentrations monitored by Japan:
Bottom sediment: from below the detection limit of 0.01 to 0.40 mg/kg.
Fish: from below the detection limit of 0.02 to 0.55 mg/kg.

Considering that the highest values were found only in a few of the 45 areas investigated these highest value may represent local PECs more likely than regional PECs.

The modelled concentrations are again (as with water) much higher than the monitored one for sediment and fish. The highest modelled concentrations were obtained for the production sites. The same explanation is offered for the difference between modelled and monitored data as for the PECs in water see 3.1.2 D.

Regional PECs:

$PEC_{regional,air}$	< 0.000 000 1	mg/m^3
$PEC_{regional,sediment}$	= 0.002 5	mg/kgwwt
$PEC_{regional,agric.soil}$	= 0.000 003 5	mg/kgwwt
$PEC_{regional,pore\ water\ in\ agric.soil}$	= 0.000 029	mg/l
$PEC_{regional,natural\ soil}$	= 0.000 003 4	mg/kgwwt
$PEC_{regional,industrial\ soil}$	= 0.000 43	mg/kgwwt

3.2 Effects on the Environment

3.2.1 Aquatic effects

A. Fish

Four acute tests with 3 species (Leuciscus idus melanotus, Oryzias latipes and Poecilia reticulata) are available. The LC50 (resp. LC10) is high in each case: > 500; 1000; > 3000; > 4400 mg/l. An LC50 of 1000 mg/l was chosen for further evaluations because it is the most recent data and an absolute data.

Two investigations on the early life stages of 2 species (Jordanella floridae and Salmo gairdneri) were reported. The NOECs are 500 respectively >1000 mg/l. Histological effects which occur at lower doses were not considered as they are not comparable with the scope of usual investigations of this type.

B. Daphnia

The acute $EC50_{48h}$ in Daphnia magna is > 2000 mg/l.
Results of a long term study (1) in Daphnia magna are:
$NOEC_{toxic,21d}$ = 18 mg/l; LC50 > 32 mg/l; $NOEC_{reprotox.}$ > 32 mg/l.

C. Algae

Results of a 4 days growth inhibition study (17) in Scenedesmus pannonicus: NOEC = 320 mg/l and EC50 = 940 mg/l.

D. Predicted No Effect Concentration (PNEC)

Short term tests with species of 3 trophic levels are available and in addition studies on chronic toxicity and reproduction toxicity with Daphnia, early life stage toxicity with fish and chronic toxicity with algae.

Melamine has a low acute and also low long term toxicity. The interspecies differences are not pronounced. The low bioconcentration factor gives no suspicion as to late effects after long term exposure.

The lowest short term L(E)C50 is 940 mg/l taken from the study with algae. Applying an assessment factor of 1000, as proposed by the SIDS Manual of the OECD 1996, a $PNEC_{aqua}$ of 0.94 mg/l is obtained.

Considering the lowest chronic or long term NOEC of 18 mg/l from the test with Daphnia and using an assessment factor of 10 in agreement with the SIDS Manual a somewhat higher $PNEC_{aqua}$ of 1.8 mg/l is calculated.

In summary, as the chronic tests are given more weight than the acute tests a **$PNEC_{aqua}$ = 1.8 mg/l** is estimated. This is in agreement with the EUSES programme.

3.2.2 Terrestrial effects

Short term growth studies with 4 species (Hordeum vulgare, Tritium aestivum, Raphanus sativus and Lepidum sativum) and one 14 days study with Pisum sativum/Phaseolus vulgaris were reported. The EC50s were between 530 and 1100 mg/l. The NOEC in the 14 days study was 1680 ppm.

A $PNEC_{terrestrial}$ of ca. 0.5 mg/kg is estimated using an assessment factor of 1000.

3.2.3 Other effects

Tests with activated sludge and with Nitrosomonas sp. and Pseudomonas putida were reported. The toxicity of melamine is low in each case. Results:

EC0 > 1992 mg/l for activated sludge;
EC0 > 100 mg/l for Nitrosomonas sp.;

EC10 > 10 000 mg/l for Pseudomonas putida.

3.3 Initial Assessment for the Environment

The Risk Characterisation Ratio RCR = PEC/PNEC was calculated for the most important compartment water. No remarkable risk of melamine to the local water compartment is derived when entering $PEC_{local,water}$ = 0.1 mg/l and a $PNEC_{aqua}$ = 1.8 mg/l: **$RCR_{local,water}$ = 0.056.**

When applying the EUSES programm with default inputs the whole spectrum of RCRs for the different compartments and spaces is obtained, see EUSES Compact Report in the Annex.
Most of the RCRs are < 1.0, e.g.:

$RCR_{local,soil}$	= 0.00035 to 0.011
RCR_{WWTP}	< 0.015 to 0.47
$RCR_{regional,water}$	= 0.0023
$RCR_{regional,soil}$	= 0.000 007
$RCR_{regional,sediment}$	= 0.002

Only 4 local RCRs were calculated as > 1:

$RCR_{local,water,production}$	= 5.2
$RCR_{local,sediment,production}$	= 6.6
$RCR_{local,water,formulation\ in\ polymers}$	= 1.04
$RCR_{local,sediment,formulation\ in\ polymers}$	= 1.3

Mainly the environment of the production site of melamine is involved. $PECs_{water}$ of production sites are by at least a factor of 100 lower than that calculated by EUSES, see also section 3.1.2. The resulting more realistic $RCR_{local,water}$ is below 1.0 and is in agreement with the manually calculated $RCR_{local,water}$ = 0.056.

As a consequence of the corrections applied for water, also the $RCR_{local,sediment}$ of production sites are lower than 1.

Only for plants producing polymers containing melamine as a flame retardant some minor problems could arise (according to the model calculation as two RCRs are just above 1.0) if they are neither connected to a WWTP nor release their waste water to a river with a medium or high flow rate. A coincidence of both conditions together with all the other worst case conditions of the model calculation is not likely.

In summary melamine presents a low risk to the environment.

4. HUMAN HEALTH

The EUSES programme was applied only for estimation of the indirect exposure via the environment. Insufficient input data are available for the evaluation of the situation of consumers and workers by EUSES.

4.1 Human Exposure

Occupational exposure in production or processing plants will be the most relevant human exposure. No major consumer exposures occur because most of the melamine is processed further

in the industry to mainly melamine resins. Only minor amounts of melamine itself are used in polymers or paints and could come into contact with humans.

4.1.1 Indirect exposure via the environment

The bioaccumulation potential of melamine and the aquatic concentrations are low. No remarkable contribution of food from aquatic organisms to the uptake of melamine in human is therefore expected.

With worst case assumptions:

- the highest monitored concentration in water (= ca. 1/10 $PEC_{local,water}$, see section 3.1.2) of 0.0076 mg/l is taken as the drinking water concentration,
- the highest monitored concentration in fish of 0.55 mg/kg (12) is used for calculating food intake,
- 2 l water intake per day; 0.115 kg fish intake per day; 70 kg bw, a daily intake (an estimated human exposure EHE) of ca. 0.0011 mg/kg bw is calculated. $EHE_{"monitored"}$ = 0.0011 $mg.kg^{-1}.d^{-1}$.

Results from EUSES: Local total daily intakes are highest (0.24 $mg.kg^{-1}.d^{-1}$) for the production of melamine and lowest (0.0078 $mg.kg^{-1}.d^{-1}$) for processing. Taking the evaluation in section 3.3 of the fate of the waste water of the producers into account, an EHE_{local} = 0.0024 $mg.kg^{-1}.d^{-1}$ is obtained and is about in agreement with the EHE derived from the monitored data.

EHE_{local} = 0.0024 $mg.kg^{-1}.d^{-1}$.

The regional total daily intake for humans $EHE_{regional}$ = ca. 0.00005 $mg.kg^{-1}.d^{-1}$.

4.1.2 Occupational exposure

<u>Inhalation during production</u>:
The production of melamine occurs in closed systems with at most low exposures of workers. Only in filling or cleaning operations or in emergency situations some - time limited - exposure to melamine dust may occur. No workplace exposure limit values for melamine are settled.

An estimated human exposure (EHE) is derived with the following inputs:
Duration of filling or cleaning operations: 10 h per week.
Concentration: 5 mg/m^3 (considering e.g. the general inspireable dust limit of 4 mg/m^3 of Germany).
Respiration rate: 20 m^3/d.
Body weight: 70 kg.
Complete absorption.
$EHE_{inhalation,worker,production}$ = 0.085 $mg.kg^{-1}.d^{-1}$.

<u>Inhalation during processing</u>:
Concentration of 0.1 to 1.14 mg melamine / m^3 air were monitored in 2 melamine processing plants. With 40 h operation and 1.1 mg/m^3 an $EHE_{inhalation,worker,processing}$ = 0.075 $mg.kg^{-1}.d^{-1}$ is obtained.

<u>Dermal exposure</u>:
The skin area (hands: 0.118 m^2) in contact with melamine and the thickness of the layer (0.1 mm) is taken from the EUSES defaults. Two replacements of the layer by washing per day are assumed. The mean bulk density of melamine is ca. 500 kg/m^3. The density on the skin is estimated to be 1/10 of the bulk density. An absorption of 1 % is assumed, because of the poor migration in the

rather thick layer of dust, the flaking off and the probably low penetration (because of the low partition coefficient). An $EHE_{dermal,worker}$ = 0.17 $mg.kg^{-1}.d^{-1}$ is estimated with these assumptions.

The overall exposure (inhalation + dermal + indirect via environment) is estimated to:
EHE_{worker} = 0.3 $mg.kg^{-1}.d^{-1}$.

4.1.3 Consumer exposure

Consumer exposure is considered to be low because most of the produced melamine does not reach the consumer and as no product which contains free melamine is known to be marketed. Melamine is included in polymer matrices in those products reaching the consumer.

Only 1 relevant monitored data is reported: 0.54 to 2.21 mg melamine / kg were found in lemon or orange juice, in coffee or curdled milk after extraction of melamine from compression moulds by these acidic foods at high temperatures (10). Taking 0.5 kg as the average intake of these - hot - foods per day and a body weight of 70 kg an uptake of ca. 0.007 mg melamine $kg^{-1}.d^{-1}$ is estimated.
$EHE_{oral,consumer}$ = 0.007 $mg.kg^{-1}.d^{-1}$.

The dermal (and the inhalation) exposure by e.g. contact to polymers containing melamine is considered to be negligible, as a worst case 1 % of the occupational exposure is assumed:
EHE = ca. 0.003 $mg.kg^{-1}.d^{-1}$.

The overall exposure (oral + inhalation + dermal + indirect via environment) is estimated to:
$EHE_{consumer}$ = 0.01 $mg.kg^{-1}.d^{-1}$.

4.2 Effects on Human Health

4.2.1 Acute toxicity

The acute toxicity was investigated in 9 studies in different species (rat, mouse and rabbit) and by several routes of administration. The lowest LD50s are:
$LD50_{oral, rat}$ = 3161 mg/kg bw.
$LC50_{inhal.,rat}$ = 3.2 mg/l.
$LD50_{dermal,rabbit}$ > 1000 mg/kg bw.
$LD50_{i.p.,mouse}$ = 112 mg/kg bw.

Melamine is not irritating to the skin and eye of rabbits and also to the skin of guinea pigs. Melamin is not a sensitizer in a human patch test and in a study with guinea pigs.

4.2.2 Repeated dose toxicity

Six studies with rats, oral administration of melamine with the feed and dosing periods of 14 days to 3 months are available. Additional studies with mice and also rather old studies with intraperitoneal administration, and rabbits and dogs were also reported.

Summarised findings of the different studies are: Depression of body weight gain and elevated water intake were observed at higher doses of ≥ ca. 500 $mg.kg^{-1}.d^{-1}$. The target organ system is the urinary tract. Melamine has a diuretic effect, it produces urinary bladder stones (urolithiasis), hyperplastic epithelial changes of the urinary bladder and calcerous deposits in the proximal kidney tubules. In mice ulceration as well as hyperplasias of the bladder occurred. Changes in the urinary

bladder were noted in the studies depending on the dose and the species used. A GLP 28 days study in rats (19) to evaluate urolithiasis indicated a dose dependent incidence of urinary bladder calculi and hyperplasia.The rat and especially the male rat is more susceptible than the mouse.

Ca. 63 and 240 $mg.kg^{-1}.d^{-1}$ are regarded as the lowest NOELs from a 13 weeks study (11) and a 28 days study (19). This applies also for stone formation. Long term studies, see 4.2.4, give a higher NOEL of 126 mg/kg bw in male rats than the 13 weeks study so that no further safety factor has to be applied, when taking NOEL = ca. 63 $mg.kg^{-1}.d^{-1}$ also for long term exposure.

4.2.3 Genotoxicity

A lot of studies with different endpoints (point mutation, chromosome aberration, DNA damage, cell transformation) and with different organisms and cells were performed. The studies included the usually performed assays as Ames test (6 studies), micronucleus test (2 studies), cytogenetics in vitro, HGPRT assay, etc. but also some not as common assays as e.g. a bioluminescence assay.

20 out of the 22 available studies were negative. 1 sister chromatid exchange test with CHO cells was equivocal as 1 of 2 trials without metabolic activation was positive. Another sister chromatid exchange test was negative.

The microscreen assay with lambda prophage induction in E. coli was positive with and without metabolic activation. This test is one of the assays which is not as common as others and where the relevance of the results still lacks a broad acceptance. Not much weight is therefore given to the result.

Altogether melamine is considered to be not genotoxic and not mutagenic.

4.2.4 Carcinogenicity

Additionally to the diuretic effect, the bladder stones and the hyperplastic epithelial changes of the urinary bladder already described under "repeated dose toxicity" long term effects were noted. These are inflammation and the occurence of transitional cell papillomas and carcinomas of the urinary bladder and chronic inflammation of the kidney.

The most relevant carcinogenicity studies are those performed by the National Toxicology Programme (NTP) with rats and mice (11). Melamine was added to the feed in 2 concentrations in each of the studies. The study duration was 2 years for rats and mice. Results that are relevant to the carcinogenicity were:

Male rats: Survival of the high dosed animals was reduced. The urinary bladder was the primary site affected. Transitional cell carcinomas were detected in the high dosed group (4500 ppm, ca. 263 mg/kg bw). The low dose (2250 ppm, ca. 126 mg/kg bw) was also the NOEL. An increased incidence of bladder stones was detected in the high dosed animals. There is a correlation between the formation of bladder calculi and bladder tumours.

Female rats: No transitional cell carcinoma or other neoplasms of the bladder and no bladder stone were observed in any of the animals. Chronic inflammation of the kidney was observed in both dosed groups (4500 ppm and 9000 ppm). The NOEL is below 4500 ppm (ca. 262 mg/kg bw).

Male mice: Survival of the high dosed animals was reduced. No neoplastic substance related lesions were found. The incidences of bladder stones, acute and chronic inflammation and epithelial

hyperplasia of the urinary bladder were increased in both dosed groups (2250 and 4500 ppm). The NOEL is below 2250 ppm (ca. 327 mg/kg bw).

Female mice: No neoplastic substance related lesions were found. 4/50 animals of the high dosed group (4500 ppm) had bladder stones. No other lesions associated with melamine were detected. The NOEL is 2250 ppm (ca. 523 mg/kg bw).

A second 2-2.5 years carcinogenicity study (6) with rats and mixing of melamine to the feed was performed with lower doses (m: 100, 500 and 1000 ppm. f: 100, 1000, 2000 ppm). No increased incidences of urinary bladder tumours and urinary bladder calculi were detected in both sexes. The NOEL is not stated and is also not quite clear from the report, probably it is the high dose. The study is not as relevant as the NTP studies because the tumours possibly occurring above 1000 respectively 2000 ppm could not be recorded.

A third 2 years carcinogenicity study of 1953 with rats and mixing melamine to the diet is outdated and not relevant. At 10 000 ppm increased incidences of bladder stones and bladder papillomas but no melamine related neoplasms were found.

Another study (15) with the main purpose to demonstrate a possible relationship of calculus formation and carcinogenesis in the urinary bladder was performed with male rats only and administration of melamine (or thymine) over 36 weeks to the feed. Doses used: 3 000, 10 000 and 30 000 ppm. Bladder weight was increased in the mid and high dosed group. Significantly increased incidences of papillary or nodular hyperplasia, of papillomatosis and of calculi of the urinary bladder were found in the mid and high dosed group. Significantly increased incidences of papillomas and carcinomas of the urinary bladder were detected only in the high dosed group. A few papillomas and carcinomas were observed in the ureter of the high dosed animals. A significant correlation between calculus formation and tumour incidence was found. It is concluded that (thymine or) melamine-induced calculi per se can induce carcinomas in the urinary bladder. The NOEL is not stated but is derived from the data to be 3000 ppm. The conversion to mg/kg bw is uncertain, as the mean body weight is not reported. An estimated mean body weight of 400 g would give ca. 110 mg/kg bw (as reported in the Full SIDS Dossier); when applying the default conversion factor of the EUSES programme a NOEL of 150 mg/kg bw would be obtained.

Further studies were performed to investigate the mechanism of bladder tumour formation:

- Addition of NaCl to a melamine containing diet can suppress the formation of calculi and reduce the incidence of transitional cell papillomas and carcinomas compared to the same melamine dose alone. The suppression is due to the induction of polyuria by NaCl. The proposed sequence of effects is: polyuria - decreased formation of calculi - reduced irritative stimulation of the epithelium - reduced proliferative lesions - lower incidence of tumours. Conclusion: The formation of bladder stones is essential for the tumour induction (14).
- In an initiation-promotion experiment melamine did not act as an initiating agent in mouse skin (17).
- An association between the formation of bladder stones and bladder neoplasms in rats was also found with other substances (7).

Several evaluations of the results of the carcinogenicity studies were performed (5), (9) and (3). The conclusions are:

- The formation of bladder stones and the resulting irritation of the bladder epithelium are necessary for the tumour induction. Melamine is only indirectly responsible for the occurrence of bladder tumours.

- The incidence of calculi is dose dependent.
- Bladder tumours were only observed in the male rat and not in female rats or mice of both sexes.
- An experiment did not reveal melamine as a tumour initiator.
- Melamine is not genotoxic. The mechanism for the tumour production is a non-genotoxic one.
- A threshold for the formation of neoplasms can therefore be established.

The recent overall evaluation of the IARC (20) is: "In making its overall evaluation, the Working Group noted that the non-DNA-reactive mechanism by which melamine produced urinary bladder tumours in male rats occurred only under conditions in which calculi were produced. Melamine is *not classifiable as to its carcinogenicity to humans (Group 3)*."

The threshold is taken as the NOEL of ca. 126 mg/kg bw from the NTP long term study with male rats. $Threshold_{carcinogenicity}$ = 126 $mg.kg^{-1}.d^{-1}$.

4.2.5 Reproduction / developmental toxicity

No indication of an effect to the reproductive organs was obtained from the repeated dose and chronic toxicity studies: Mammary glands, ovaries, prostate, seminal vesicles, testes and uterus were examined macroscopically and microscopically in 13-weeks and in chronic toxicity studies with rats and mice (11) and were found to be unaffected by melamine at each of the doses used. The lowest NOEL for general toxicity in these studies was ca. 63 $mg.kg^{-1}.d^{-1}$, see also 4.2.2 and 4.2.4.

Melamine is not teratogenic in an investigation with rats (8). The NOEL for the foetuses is ca. 1060 $mg.kg^{-1}.d^{-1}$ based on no findings in the high dose used. A NOEL of ca. 400 $mg.kg^{-1}.d^{-1}$ (the medium dose in this study) is based on the maternal toxicity. Decreased body weight and feed consumption and haematuria of the dams were signs of maternal toxicity.

4.2.6 Toxicokinetics

Melamine is not metabolized and is rapidly eliminated via urine in a study with oral application to rats. The elimination half-life in plasma is about 3 hours.

4.3 Initial Assessment for Human Health

Sufficient data on the exposure and the effects are available to perform an initial risk assessment of melamine.

The lowest NOEL from the different toxicity studies is 63 $mg.kg^{-1}.d^{-1}$.

The NOEL for the carcinogenicity study was higher (ca. 126 $mg.kg^{-1}.d^{-1}$), a threshold for bladder stones and therefore for tumours at 126 $mg.kg^{-1}.d^{-1}$ is likely to exist so that the margin of safety for the critical property "carcinogenicity" is even higher by a factor of 2 than that calculated in the next sections from the general toxicity of melamine.

4.3.1 Occupational risk

Inhalation and dermal contact of dust are considered to be the main routes of intake of melamine.

The NOEL of 63 $mg.kg^{-1}.d^{-1}$ is 210 times higher than the estimated overall human exposure (EHE) of 0.3 $mg.kg^{-1}.d^{-1}$ (see section 4.1.2).

A margin of safety (MOS) = NOEL/EHE is calculated:
MOS_{worker} = 210.
$MOS_{worker,carcinogenicity}$ = 420.

Other possible effects, i.e. irritation to the skin and eye, sensitisation, mutagenicity and teratogenicity do not present a relevant risk.

It is concluded that workers are of low risk.

4.3.2 Consumer risk

An overall human exposure of 0.01 $mg.kg^{-1}.d^{-1}$, see section 4.1.3 was estimated.
$MOS_{consumer}$ = 6000.
$MOS_{consumer,carcinogenicity}$ = 12000.

Other possible effects, i.e. irritation to the skin and eye, sensitisation, mutagenicity and teratogenicity do not present a relevant risk.

It is concluded that consumers are of low risk.

5. CONCLUSIONS AND RECOMMENDATIONS

5.1 Conclusions

Melamine is produced in large amounts on few sites. Its main use is as an intermediate in the synthesis of melamine resins.

Environment:

The outstanding physical-chemical property concerning the risk assessment is a low n-octanol/water partition coefficient. Melamine is not readily biodegradable but adapted waste water treatment plants can degrade it effectively. Water is the most relevant compartment in the environmental fate of the substance.

The ecotoxicity is low, data are available from different species and different trophic levels.

The environmental exposure estimations were based on some monitored concentrations and on the EUSES model. No relevant risk was detected for the environment. Most of the estimated risk characterisation ratios (PEC/PNEC) were lower than 1. Those few modelled risk characterisation ratios beeing slightly above 1 could be revised (and lowered to < 1) by assuming realistic worst case conditions.

Therefore, melamine is currently considered of low potential risk.

Health:

The toxicity to mammals is also low. Studies ranging from skin irritation to carcinogenicity are available. Melamine is not genotoxic but it causes carcinomas of the urinary bladder at high doses in male rats only. Formation of bladder stones occurred and these calculi are necessary for the induction of tumours. Carcinomas are induced by continuous irritation of the bladder epithelium by

the calculi, so that melamine acts only indirectly as a non-genotoxic carcinogen. A threshold concept can be used. Melamine is not irritating to skin and eye, not sensitising and not teratogenic.

No relevant risk was detected for humans. The estimated margin of safety for workers is at least 210, that for consumers at least 6000.

Therefore, melamine is currently considered of low potential risk.

5.2 Recommendations

Melamine is presently of low priority for further work.
No further testing is required.
No risk reduction measures are proposed.

6. REFERENCES

(1) Adema, D.M.M., The acute and chronic toxicity of melamine to Daphnia magna, TNO-report, prepared on behalf of DSM Central Laboratory, 1-10, Report no. CL 78/60, 1978.

(2) Biodegradation and Bioaccumulation Data of Existing Chemicals Based on the CSCL Japan, ed. by Chemicals Inspection and Testing Institute Japan, published by Japan Chemical Industry Ecology-Toxicology and Information Center, October 1992.

(3) Cohen S.M. and Lawson T.A., Rodent bladder tumors do not always predict for humans, Cancer Lett. 93, 9-16, 1995.

(4) Crews G.M., Ripperger W., Kersebohm D.B. and Seeholzer J., Melamine and Guanamines, in Ullmann's Encyclopedia of Industrial Chemistry, Vol A16, p. 171-185, 5th ed., VCH Verlagsgesellschaft, 1990.

(5) FDA Cancer Assessment Committee, 1984.

(6) Hazelton Raltech Report for American Cyanamid Company, 2-Year chronic feeding study of melamine in Fisher 344 rats, unpublished data, 1983.

(7) Heck H.A. und Tyl R.W., The induction of bladder stones by tereohthalic acid, dimethyl terephthalate, and melamine and its relevance to risk assessment, Regulat. Tox. Pharmacol. 5, 294-313, 1985.

(8) Hellwig J., Gembrandt Ch. Hildebrandt B., Melamine - Prenatal Toxicity in Wistar Rats after oral Administration (Diet), Project No. 32R0242/94007, 1996.

(9) IARC Monographs on the evaluation of the carcinogenic risk of chemicals to humans, Vol. 39, 1985.

(10) Ishiwata H. et al., Liquid chromatographic determination of melamine in beverages, J. Assoc. Off. Anal. Chem., 70, 457-460, 1987.

(11) Melnick R.L. et al., Urolithiasis and bladder carcinogenicity of melamine in rodents, Toxicol.Appl.Pharmacol. 72, 292-303, 1984.

(12) Office of Health Studies, Chemicals in the Environment, Report on Environmental Survey and Wildlife Monitoring of Chemicals in F.Y. 1986 and 1987, Department of Environmental Health, Japan, 1989.

(13) Office of Health Studies, Chemicals in the Environment, Report on Environmental Survey and Wildlife Monitoring of Chemicals in F.Y. 1988 and 1989, Department of Environmental Health, Japan, 1991.

(14) Office of Health Studies, Chemicals in the Environment, Report on Environmental Survey and Wildlife Monitoring of Chemicals in F.Y. 1995, Department of Environmental Health, Japan, 1997.

(15) Ogasawara H. et al., Urinary bladder carcinogenesis induced by melamine in F344 male rats: correlation between carcinogenicity and urolith formation, Carcinogenesis 16, 2773-2777, 1995.

(16) Okumura M. et al., Relationship between calculus formation and carcinogenesis in the urinary bladder of rats administered the non-genotoxic agents, thymine or melamine, Carcinogenesis 13, 1043-1045, 1992.

(17) Oldersma H., Hanstveit A.O., The effect of the product melamine on the growth of the green alga Scenedesmus pannonicus, TNO-report no. 81/188, 1-12, 1982.

(18) Perrella F.W. und Boutwell R.K., Triethylenemelamine: an initiator of two stage carcinogenesis in mouse skin which lacks the potential of a complete carcinogen, Canc.Letters 21, 37-41, 1983.

(19) RTI, Evaluation of urolithiasis induction by melamine in male weanling Fischer 344 rats, Project No. 31T-2407 for American Cyanamid Company, unpublished data, 1982.

(20) Wilbourn, J.D., IARC - WHO, personal communication, 30 November 1998.

ANNEXES

- EUSES Compact Report.
- Full SIDS Dossier.

EUSES Compact report	Single substance
Printed on	1998.08.18 16:04:39
Study	Melamine
Substance	Melamine
Defaults	Standard
Assessment types	1A, 1B, 2, 3A, 3B
Base set complete	No
Explanation status column	'O' = Output; 'D' = Default; 'S' = Set; 'I' = Imported

Name	Value	Units	Status
STUDY			
STUDY IDENTIFICATION			
Study name Melamine			S
Study description OECD HPV			S
Author Heinz Hofer			S
Institute Austrian Research Center Seibersdorf			S
Address			D
Zip code A-2444			S
City Seibersdorf			S
Country Austria			S
Telephone ** 43 2254 780 3501			S
Telefax ** 43 2254 780 3653			S
Email heinz.hofer@arcs.ac.at			S
Calculations checksum43924A97			S
SUBSTANCE			
SUBSTANCE IDENTIFICATION			
General name Melamine			S
Description 1,3,5-Triazine-2,4,6-triamine			S
CAS-No 108-78-1			S
EC-notification no.			D
EINECS no. 203-615-4			S
PHYSICO-CHEMICAL PROPERTIES			
Molecular weight	126.13	[g.mol-1]	S
Melting point	350	[oC]	S
Boiling point	>350	[oC]	S
Vapour pressure at 25 [oC]	1.1E-07	[Pa]	S
Octanol-water partition coefficient.	-1.14	[log10]	S
Water solubility	3.1E+03	[mg.l-1]	S
RELEASE ESTIMATION			
CHARACTERIZATION AND TONNAGE			
High Production Volume Chemical	Yes		S
Production volume of chemical in EU	2.5E+05	[tonnes.yr-1]	S
Volume of chemical imported to EU	0	[tonnes.yr-1]	D
Volume of chemical exported from EU	0	[tonnes.yr-1]	D
Intermittent release	No		D
USE PATTERNS			
EMISSION INPUT DATA [USE PATTERN 1]			
Industry category	3 Chemical industry:		S

	chemicals used in synthesis		
Use category	33 Intermediates		S
Emission scenario document available	Yes		O
Extra details on use category	Substance processed elsewhere		S
Extra details on use category	No extra details necessary		S
Fraction of tonnage for application	0.97	[-]	S
Fraction of chemical in formulation	1E-20	[-]	S
Production	Yes		S
Formulation	No		S
Processing	Yes		S
Private use	No		S
Recovery	No		S
Main category production	Ic Intermed. stored off-site/dedicated equip.		S
Main category formulation	III Multi-purpose equipment		S
Main category processing	Ib Continuous production process		S
EMISSION INPUT DATA [USE PATTERN 2]			
Industry category	11 Polymers industry		S
Use category	22 Flame-retardants and fire preventing agents		S
Emission scenario document available	No		O
Extra details on use category	Polymer processing		S
Extra details on use category	Thermoplastics: additives, pigments, fillers		S
Fraction of tonnage for application	0.028	[-]	S
Fraction of chemical in formulation	0.1	[-]	S
Production	No		O
Formulation	Yes		S
Processing	No		S
Private use	Yes		S
Recovery	No		S
Main category production	III Multi-purpose equipment		D
Main category formulation	Ib Dedicated equipment, (very) little cleaning		S
Main category processing	III Non-dispersive use		S
EMISSION INPUT DATA [USE PATTERN 3]			
Industry category	14 Paints, lacquers and varnishes industry		S
Use category	22 Flame-retardants and fire preventing agents		S
Emission scenario document available	Yes		O
Extra details on use category	Water based		S
Extra details on use category	Constructions, maintenance, etc.		S
Fraction of tonnage for application	4E-03	[-]	S
Fraction of chemical in formulation	0.1	[-]	S
Production	No		S
Formulation	Yes		S
Processing	No		S
Private use	Yes		S
Recovery	No		S
Main category production	III Multi-purpose equipment		S
Main category formulation	Ib Dedicated equipment, (very) little cleaning		S
Main category processing	II Inclusion into or onto a matrix		S

DEGRADATION AND TRANSFORMATION RATES

CHARACTERIZATION AND STP			
Characterization of biodegradability	Not biodegradable		S
Degradation calculation method in STP	First order, standard OECD/EU tests		S
Rate constant for biodegradation in STP	0	[d-1]	O
Total rate constant for degradation in STP	0	[d-1]	O
Maximum growth rate of specific microorganisms	2	[d-1]	D
Half saturation concentration	0.5	[g.m-3]	D
ENVIRONMENTAL			
Specific degradation rate constant with OH-radicals	0	[cm3.molec-1.s-1]	D
Rate constant for degradation in air	0	[d-1]	O
Rate constant for hydrolysis in surface water	6.93E-07	[d-1]	O
Rate constant for photolysis in surface water	6.93E-07	[d-1]	O
Rate constant for biodegradation in surface water	0	[d-1]	O
Total rate constant for degradation in bulk surface water	1.39E-06	[d-1]	O
Rate constant for biodegradation in bulk soil	6.93E-07	[d-1]	O
Total rate constant for degradation in bulk soil	6.93E-07	[d-1]	O
Rate constant for biodegradation in aerated sediment	6.93E-07	[d-1]	O
Total rate constant for degradation in bulk sediment	6.93E-08	[d-1]	O

EFFECTS

INPUT OF EFFECTS DATA

MICRO-ORGANISMS			
EC50 for micro-organisms in a STP	>1.992E+03	[mg.l-1]	S
Specific bacterial population?	No		S
EC10 for micro-organisms in a STP	>1.992E+03	[mg.l-1]	S
Specific bacterial population?	No		S
NOEC for micro-organisms in a STP	>1.992E+03	[mg.l-1]	S
Specific bacterial population?	No		S
AQUATIC ORGANISMS			
LC50 for fish	1000	[mg.l-1]	S
L(E)C50 for Daphnia	>2E+03	[mg.l-1]	S
EC50 for algae	940	[mg.l-1]	S
LC50 for other aquatic species	??	[mg.l-1]	D
Species	other		D
NOEC for fish	500	[mg.l-1]	S
NOEC for Daphnia	18	[mg.l-1]	S
NOEC for algae	320	[mg.l-1]	S
NOEC for other aquatic species	??	[mg.l-1]	D
Additional aquatic NOEC	??	[mg.l-1]	D
Additional aquatic NOEC	??	[mg.l-1]	D
Additional aquatic NOEC	??	[mg.l-1]	D
Additional aquatic NOEC	??	[mg.l-1]	D
Additional aquatic NOEC	??	[mg.l-1]	D
Additional aquatic NOEC	??	[mg.l-1]	D
TERRESTRIAL ORGANISMS			
LC50 for plants	530	[mg.kgwwt-1]	S
LC50 for earthworms	??	[mg.kgwwt-1]	D
EC50 for microorganisms	??	[mg.kgwwt-1]	D
LC50 for other terrestrial species	??	[mg.kgwwt-1]	D
Species	other		D
NOEC for plants	1.68E+03	[mg.kgwwt-1]	S
NOEC for earthworms	??	[mg.kgwwt-1]	D
NOEC for microorganisms	??	[mg.kgwwt-1]	D
NOEC for other terrestrial species	??	[mg.kgwwt-1]	D
NOEC for other terrestrial species	??	[mg.kgwwt-1]	D
Additional terrestrial NOEC	??	[mg.kgwwt-1]	D
Additional terrestrial NOEC	??	[mg.kgwwt-1]	D
Additional terrestrial NOEC	??	[mg.kgwwt-1]	D
Additional terrestrial NOEC	??	[mg.kgwwt-1]	D
Additional terrestrial NOEC	??	[mg.kgwwt-1]	D
Additional terrestrial NOEC	??	[mg.kgwwt-1]	D

BIRDS			
LC50 in avian dietary study (5 days)	??	[mg.kg-1]	D
NOAEL	??	[mg.kg-1.d-1]	D
NOEC via food	??	[mg.kg-1]	O
Duration of (sub-)chronic oral test	Chronic		S
Conversion factor NOAEL to NOEC	8	[kg.d.kg-1]	D
MAMMALS			
ACUTE			
Oral LD50	3.16E+03	[mg.kg-1]	S
Oral Discriminatory Dose	??	[mg.kg-1]	D
Dermal LD50	>1E+03	[mg.kg-1]	S
Inhalatory LC50	3.2E+03	[mg.m-3]	S
(SUB)CHRONIC			
Oral NOAEL	63	[mg.kg-1.d-1]	S
Oral LOAEL	??	[mg.kg-1.d-1]	O
Inhalatory NOAEL	294	[mg.m-3]	O
Inhalatory LOAEL	??	[mg.m-3]	O
Dermal NOAEL	63	[mg.kg-1.d-1]	O
Dermal LOAEL	??	[mg.kg-1.d-1]	O
NOEC via food	630	[mg.kg-1]	O
LOEC via food	??	[mg.kg-1]	D
Duration of (sub-)chronic oral test	90 days		S
Species for conversion of NOAEL to NOEC	Rattus norvegicus (<6 weeks)		S
Conversion factor NOAEL to NOEC	10	[kg.d.kg-1]	O
HUMANS			
(SUB)CHRONIC			
Oral NOAEL	??	[mg.kg-1.d-1]	D
Oral LOAEL	??	[mg.kg-1.d-1]	D
Dermal NOEC in a medium	??	[mg.cm-3]	D
Dermal LOEC in a medium	??	[mg.cm-3]	D
Inhalatory (fibre) NOAEL	??	[fibres.m-3]	D
Inhalatory (fibre) LOAEL	??	[fibres.m-3]	D
Dermal LOAEL	??	[mg.kg-1.d-1]	O
Dermal NOAEL	??	[mg.kg-1.d-1]	O
Inhalatory LOAEL	??	[mg.m-3]	O
Inhalatory NOAEL	??	[mg.m-3]	O

CURRENT CLASSIFICATION			
Corrosive (C, R34 or R35)	No		S
Irritating to skin (Xi, R38)	No		S
Irritating to eyes (Xi, R36)	No		S
Risk of serious damage to eyes (Xi, R41)	No		S
Irritating to respiratory system (Xi, R37)	No		S
May cause sensitisation by inhalation (Xn, R42)	No		S
May cause sensitisation by skin contact (Xi, R43)	No		S
May cause cancer (T, R45)	No		S
May cause cancer by inhalation (T, R49)	No		S
Possible risk of irreversible effects (Xn, R40)	No		S

ENVIRONMENTAL EFFECTS ASSESSMENT

INTERMEDIATE RESULTS AQUATIC ORGANISMS, MICRO-ORGANISMS AND PREDATORS

Toxicological data used for extrapolation to PNEC Aqua	18	[mg.l-1]	O
Assessment factor applied in extrapolation to PNEC Aqua	10	[-]	O
Toxicological data used for extrapolation to PNEC Aqua	940	[mg.l-1]	O
Assessment factor applied in extrapolation to PNEC Aqua	100	[-]	O
Toxicological data used for extrapolation to PNEC micro	>1.99E+03	[mg.l-1]	O
Assessment factor applied in extrapolation to PNEC micro	10	[-]	O
Toxicological data used for extrapolation to PNEC oral	630	[mg.kg-1]	O

Assessment factor applied in extrapolation to PNEC oral	30	[-]	O

INTERMEDIATE RESULTS TERRESTRIAL AND SEDIMENT ORGANISMS

Toxicological data used for extrapolation to PNEC Terr	530	[mg.kgwwt-1]	O
Assessment factor applied in extrapolation to PNEC Terr	1000	[-]	O
Equilibrium partitioning used for PNEC in soil?	No		O
Equilibrium partitioning used for PNEC in sediment?	Yes		O

PNECS FOR AQUATIC ORGANISMS, MICRO-ORGANISMS AND PREDATORS

PNEC for aquatic organisms	1.8	[mg.l-1]	O
PNEC for aquatic organisms, intermittent releases	9.4	[mg.l-1]	O
PNEC for micro-organisms in a STP	>199	[mg.l-1]	O
PNEC for secondary poisoning of birds and mammals	21	[mg.kg-1]	O
PNEC for aquatic organisms with statistical method	??	[mg.l-1]	O

PNECS FOR TERRESTRIAL AND SEDIMENT ORGANISMS

PNEC for terrestrial organisms	0.53	[mg.kgwwt-1]	O
PNEC for terrestrial organisms with statistical method	??	[mg.kgwwt-1]	O
PNEC for sediment-dwelling organisms	1.11	[mg.kgwwt-1]	O

RISK CHARACTERIZATION
ENVIRONMENTAL EXPOSURE

LOCAL

RISK CHARACTERIZATION OF [USE PATTERN 1] [PRODUCTION]
ENVIRONMENTAL

RCR for the local water compartment	5.21	[-]	O
Intermittent release	No		D
RCR for the local soil compartment	0.0106	[-]	O
Extra factor 10 applied to PEC	No		O
RCR for the local sediment compartment	6.62	[-]	O
Extra factor 10 applied to PEC	No		O
RCR for the sewage treatment plant	<0.471	[-]	O

PREDATORS

RCR for fish-eating birds and mammals	0.259	[-]	O
RCR for worm-eating birds and mammals	2.2E-04	[-]	O

HUMANS

MOS local, total exposure via all media	264	[-]	O
MOS local, exposure via air	7.58E+13	[-]	O

RISK CHARACTERIZATION OF [USE PATTERN 1] [PROCESSING]
ENVIRONMENTAL

RCR for the local water compartment	0.171	[-]	O
Intermittent release	No		D
RCR for the local soil compartment	3.49E-04	[-]	O
Extra factor 10 applied to PEC	No		O
RCR for the local sediment compartment	0.217	[-]	O
Extra factor 10 applied to PEC	No		O
RCR for the sewage treatment plant	<0.0152	[-]	O

PREDATORS

RCR for fish-eating birds and mammals	8.66E-03	[-]	O
RCR for worm-eating birds and mammals	7.64E-06	[-]	O

HUMANS

MOS local, total exposure via all media	8.04E+03	[-]	O
MOS local, exposure via air	1.85E+15	[-]	O

RISK CHARACTERIZATION OF [USE PATTERN 2] [FORMULATION]

ENVIRONMENTAL			
RCR for the local water compartment	1.04	[-]	O
Intermittent release	No		D
RCR for the local soil compartment	3.07E-03	[-]	O
Extra factor 10 applied to PEC	No		O
RCR for the local sediment compartment	1.32	[-]	O
Extra factor 10 applied to PEC	No		O
RCR for the sewage treatment plant	<0.0937	[-]	O
PREDATORS			
RCR for fish-eating birds and mammals	0.0519	[-]	O
RCR for worm-eating birds and mammals	8.44E-05	[-]	O
HUMANS			
MOS local, total exposure via all media	867	[-]	O
MOS local, exposure via air	1.38E+06	[-]	O
RISK CHARACTERIZATION OF [USE PATTERN 3] [FORMULATION]			
ENVIRONMENTAL			
RCR for the local water compartment	0.188	[-]	O
Intermittent release	No		D
RCR for the local soil compartment	5.54E-04	[-]	O
Extra factor 10 applied to PEC	No		O
RCR for the local sediment compartment	0.238	[-]	O
Extra factor 10 applied to PEC	No		O
RCR for the sewage treatment plant	<0.0167	[-]	O
PREDATORS			
RCR for fish-eating birds and mammals	9.5E-03	[-]	O
RCR for worm-eating birds and mammals	1.55E-05	[-]	O
HUMANS			
MOS local, total exposure via all media	4.81E+03	[-]	O
MOS local, exposure via air	7.72E+06	[-]	O
REGIONAL			
ENVIRONMENT			
RCR for the regional water compartment	2.34E-03	[-]	O
RCR for the regional soil compartment	6.57E-06	[-]	O
Extra factor 10 applied to PEC	No		O
RCR for the regional sediment compartment	2.28E-03	[-]	O
Extra factor 10 applied to PEC	No		O
HUMANS			
MOS regional, total exposure via all media	4.82E+05	[-]	O
MOS regional, exposure via air	8.45E+15	[-]	O

FULL SIDS DOSSIER
ON THE HPV PHASE 2 CHEMICAL

MELAMINE

CAS No. 108-78-1

Sponsor Country : Austria

Last Revision Date: 26 February 1999

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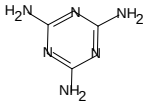
SIDS PROFILE
DATE: 19 August 1998

1.01 A.	**CAS No.**	108-78-1
1.01 C.	**CHEMICAL NAME (OECD Name)**	1,3,5-Triazine-2,4,6-triamine
1.01 D.	**CAS DESCRIPTOR**	s-Triazine; 4,6-diamino-1,2-dihydro-2-imino-
1.01 E.	**EINECS No.**	203-615-4.
1.01 G.	**STRUCTURAL FORMULA**	
1.5	**QUANTITY**	Worldwide production of ca. 600 000 t/a in 1996. Ca. 30 producers.
1.7	**USE PATTERN**	The main use (ca. 97 %) of melamine is the production of melamine resins or other melamine compounds. Melamine resins and compounds are used e.g. in laminates, glues, adhesives, molding compounds, etc. Melamine itself is used as a flame retardant in polyurethan foams in UK (2.8 %) and possibly for some other minor applications (0.4 %) as e.g. in paints for fire protection.
1.9	**SOURCES AND LEVELS OF EXPOSURE**	0.4 kg nitrogen in the waste water per ton of melamine produced; 0.02 kg nitrogen after the waste water treatment plant. Emission to air: < 100 kg / a at the production site (ca. 40 000 t / a) and < 50 kg /a at the processing site. Concentrations monitored in rivers of Japan: water: 0.0 - 0.0076 ppm, bottom sediment: 0.0 - 0.32 ppm, fish: 0.0 - 0.55 ppm.
ISSUES FOR DISCUSSION	SIDS testing has been required in 1993: A developmental toxicity / teratogenicity study has been performed according to the SIDS testing plan.	

SIDS SUMMARY

DATE: 19 August 1998

CAS NO: 108-78-1		Information	OECD Study	GLP	Other Study	Estimation Method	Acceptable	SIDS Testing Required
STUDY		**Y/N**	**Y/N**	**Y/N**	**Y/N**	**Y/N**	**Y/N**	**Y/N**
PHYSICAL-CHEMICAL DATA								
2.1	Melting point	Y	N		Y	N	Y	N
2.2	Boiling point	Y	/	/	/	/	/	N
2.3	Density	Y	N		Y	N	Y	N
2.4	Vapour pressure	Y	N		Y	N	Y	N
2.5	Partition coefficient	Y	Y		/	N	Y	N
2.6	Water solubility	Y	N		Y	N	Y	N
	pH and pKa values	Y	N		Y	N	Y	N
2.12	Oxidation: reduction potential	N	/		/	/	/	N
	OTHER P/C STUDIES RECEIVED	Y						
ENVIRONMENTAL FATE and PATHWAY								
3.1.1	Photodegradation	Y	N		Y	N	Y	N
3.1.2	Stability in water	N	/	/	/	/	Y	N
3.2	Monitoring data	Y	N		Y	N	Y	N
3.3	Transport and distribution	Y	N		Y	Y	Y	N
3.5	Biodegradation	Y	N		Y	N	Y	N
	OTHER ENV FATE STUDIES RECEIVED	Y						
ECOTOXICITY								
4.1	Acute toxicity to fish	Y	N		Y	N	Y	N
4.2	Acute toxicity to Daphnia	Y	N		Y	N	Y	N
4.3	Toxicity to algae	Y	N		Y	N	Y	N
4.5.2	Chronic toxicity to Daphnia	Y	N		Y	N	Y	N
4.6.1	Toxicity to soil dwelling organisms	N	/	/	/	/	/	N
4.6.2	Toxicity to terrestrial plants	Y	N		Y	N	Y	N
4.6.3	Toxicity to birds	N	/	/	/	/	/	N
	OTHER ECOTOXICITY STUDIES RECEIVED	Y						
TOXICITY								
5.1.1	Acute oral	Y	N		Y	N	Y	N
5.1.2	Acute inhalation	Y	N		Y	N	Y	N
5.1.3	Acute dermal	N	/	/	/	/	/	N
5.4	Repeated dose	Y	N	Y/N	Y	N	Y	N
5.5	Genetic toxicity *in vitro*						Y	
	Gene mutation	Y	N	Y/N	Y	N	Y	N
	Chromosomal aberration	Y	N	Y/N	Y	N	Y	N
5.6	Genetic toxicity *in vivo*	Y	N	Y/N	Y	N	Y	N
5.8	Reproduction toxicity	N	/	/	/	/		N
5.9	Development / teratogenicity	Y	Y	Y	Y	N	Y	N
5.11	Human experience	Y	N	N	Y	N	Y	N
	OTHER TOXICITY STUDIES RECEIVED	Y						

1. GENERAL INFORMATION

General reviews on melamine are found for example in (4) and (76).

Reviews on the risk of melamine and / or compilation of the hazard are reported in (36), (45), (9), (49), (105) and (47).

1.01 Substance Information

A. CAS number: 108-78-1

B. Name *(IUPAC)*: 1,3,5-Triazine-2,4,6-triamine (9CI)

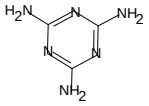
C. Name *(OECD)*: 1,3,5-Triazine-2,4,6-triamine

D. CAS Descriptor: s-Triazine; 4,6-diamino-1,2-dihydro-2-imino-

E. EINECS-Number: 203-615-4

F. Molecular Formula: $C_3N_6H_6$

G. Structural Formula:



H. Substance Group *(only for petroleum products)*: /

I. Substance Remarks: /

J. Molecular Weight: 126.13

1.02 OECD Information

A. Sponsor Country Austria

B. Lead Organisation

Name: Bundesministerium für Umwelt, Jugend und Familie.
Contact person: MR Mag. Heinrich Kohlmann

Address:
Street: Stubenbastei 5
Postal code: A-1010
Town: Vienna
Country: Austria
Tel: **43 1 515 22 2353
Fax: **43 1 515 22 7352
E-mail: heinrich.kohlmann@bmu.gv.at

C. Responder

Name:	Agrolinz Melamin GmbH
Address:	
Street:	St.-Peter-Straße 25
Postal code:	A-4021
Town:	Linz
Country:	Austria
Tel:	**43 732 6914 3602
Fax:	**43 732 6914 2355

1.03 SIDS Dossier Development and Contributors

The SIDS Dossier was first presented at the SIDS Meeting on 23 September 1993. It was revised in 1998 and the format proposed in the SIDS Manual of the OECD was adopted.

Additional data were taken mainly from the IUCLID file on melamine (49). Data for the IUCLID file were supplied by:

Agrolinz Melamin G.m.b.H.
St. Peter-Str. 25
A-4021 Linz
Austria

Atochem
92080 Paris la Defense
France

BASF AG
Karl-Bosch-Straße
67056 Ludwigshafen
Germany

Casco Nobel AB
Box 115 38
100 61 STOCKHOLM
Sweden

Cassella AG
Hanauer Landstraße 526
60382 Frankfurt/Main
Germany

DSM Chemicals & Fertilizers BV,
(now: DSM Melamine)
P.O. Box 43
6130 AA Sittard
Netherlands

Hoechst AG
65903 Frankfurt/Main
Germany

Krems Chemie AG
Hafenstraße 77
3500 Krems
Austria

SKW Trostberg
Postfach 1262
83303 Trostberg
Germany

Supplementary data were obtained from

- BASF AG, Germany; DSM Melamine, Netherlands and Agrolinz Melamin GmbH, Austria.
- Contact Points of OECD member countries.
- Open literature.

A further revision of the document was performed in January/February 1999 after presentation of the SIDS Initial Assessment Report to the 8th SIDS Initial Assessment Meeting of the OECD on 28 to 30 October 1998.

1.1 General Substance Information

A. Type of Substance organic

B. Physical State solid (at 20 °C and 101 300 Pa)

C. Purity > 99.8 % - 99.9 % w/w (Agrolinz Melamine, Austria; BASF AG, Germany; DSM Melamine, Netherlands).

1.2 Synonyms

1,3,5-Triazine, 2,4,6-triamine
1,3,5-Triazine-2,4,6(1H,3H,5H)-triimine
1,3,5-Triazine-2,4,6-triamine (9CI)
2,4,6-Triamino - 1,3,5-Triazine
2,4,6-Triamino-1,3,5-triazin
2,4,6-Triamino-s-triazine
2,4,6-Triaminotriazine
Cyanuramide
Cyanuric Triamide
Cyanurotriamide
Cyanurotriamine
Cyanurtriamine
Isomelamine
Melamin
Melamine (8CI)
s-Triaminotriazine
s-Triazine, 4,6-diamino-1,2-dihydro-2-imino- (6CI)
s-Triazinetriamine
Triaminotriazine

1.3 Impurities

Impurities: Melem: max. 0.06 %
Ash: max. 0.01 %
Source: Agrolinz Melamin GmbH, Austria

Impurities Ammelin, ammelid, cyanuric acid: < 0.1 %
Source: (36)

1.4 Additives

No additives are used.
Source: Agrolinz Melamin GmbH, Austria

1.5 Quantity

Quantity: Worldwide consumption of ca. 600 000 t/a in 1996.
Ca. 30 producers wordwide.
Production capacity 1997:

Europe + Middle East	306 000 t/a
Asia	297 000 t/a
Americas	118 000 t/a

Demand 1996:

Europe + Middle East + Africa	285 000 t/a
Asia + Pacific	220 000 t/a
Americas	95 000 t/a

Source: (53)

Quantity: Worldwide production of ca. 600 000 t/a in 1997.
180 000 t / a by DSM Melamine, Netherlands.
Source: DSM Melamine, Netherlands.

Quantity: USA production and export: 112 000 t.
Source: OECD contact point in the USA, 1998.

Quantity: Production of 40 000 t/a by BASF.
Source: BASF AG, Germany.

Quantity: Production of 50 000 t/a at Agrolinz Melamin.
Source: Agrolinz Melamin GmbH, Austria, 1996.

Quantity: Worldwide production of ca. 550 000 t/a in 1990/91.
Ca. 18 producers wordwide.
Production capacity 1990/91:

Western Europe	230 000 t/a
Eastern Europe	50 000 t/a
America	97 000 t/a
Middle and far East	175 000 t/a

Source: (4)

1.6.1 Labelling

No labelling is required according to Directive 67/548/EEC.

1.6.2 Classification

No classification is required according to Directive 67/548/EEC.

Water pollution (German Law)

Class of danger: 1 (weakly water polluting)
Source: BASF AG Ludwigshafen; SKW Trostberg Trostberg; Hoechst AG Frankfurt/Main; Cassella AG Frankfurt/Main, Germany.

Air pollution (German Law)

Number: 3.1.7 (organic substances)

Class of danger: III
Source: SKW Trostberg; BASF AG Ludwigshafen

1.7 Use Pattern

Main categories according to the HEDSET:

a) Main category Ic (Substance produced in closed systems; isolated intermediate, stored off site):
Melamine is continuously produced in closed systems. Melamine is an isolated intermediate with controlled transport to processing sites.

b) Main category Ic (Substance processed in closed systems):
Melamine is processed in closed systems in the chemical industry to produce melamine compounds, mainly melamine resins. This is the predominant (ca. 97 %) use of melamine.

In Germany > 99.5 % are processed to resins (4).

Melamine resins or other melamine compounds are used in laminates (e.g. for tabletops), glues, adhesives, moulding compounds, coatings, paper (to obtain wet strength), textiles (to obtain shrink resistance, water repellence, stain repellence, fire retardance), flame retardants or superplastizers for concrete.

An estimation of the applications, in percent, by region is given by (53):

Application	Europe, Africa, Middle East	Americas	Asia-Pacific	World
Laminates	53	45	14	38
Glues, adhesives	24	5	50	30
Moulding compounds	6	7	18	10
Coatings	7	22	11	11
Paper and textiles resins, superplasticizers for concrete, flame retardants for polyurethane foam	10	21	7	11

c) Main category II (Inclusion into a matrix).
Melamine itself is used as a flame retardant in polyurethan foams in UK (ca. 7 000 t/a, i.e. 2.8 % of the European market) and possibly for some other minor applications (ca. 1 000 t/a, i.e. 0.4 % of the European market) as e.g. in paints for fire protection. Melamine is included into a polymer matrix in these cases.

d) Other earlier reported uses (e.g. use as a fertilizer) have not gained importance or are of no importance nowadays.

Industrial category:
a) Category 3: Chemical industry: chemicals used in synthesis.
b) Category 3: Chemical industry: chemicals used in synthesis.
c) Mainly Category 11: Polymers industry.

Use categories:
a) Category 33: Intermediate.
b) Category 33: Intermediate.
c) Category 22: Flame retardants and fire preventing agents.

References OECD contact points; (36), (4), (49), (76); melamine producers.

1.8 Occupational Exposure Limit Values

Type of limit: MAC (NL)
Limit value: 10 mg/m^3
Remark: MAC (NL) not indicated ; use nuisance dust limit.
Source: DSM Melamine, Netherlands.

Type of limit: MAK (DE)
Limit value: /
Remark: No MAK value (occupational exposure limit) is agreed on melamine.
Source: (131)

Type of limit: TLV (US)
Limit value: 10 mg/m^3
Remark: provisionally by manufacturer; TLV according to nontoxic nuisance dust TLV.
Source: (44)

1.9 Sources of Exposure

Remarks: Waste water (220 m^3 / d) of a melamine production plant contained 4 g melamine / l, that is a release of ca. 300 t melamine per year (data of 1997).
Production capacity: ca. 50 000 t / a.
The emission with waste air leaving the same production plant was 41 kg / a.
A diffuse emission within the plant during filling operations, manipulation or cleaning is estimated to 1 t melamine / a.
Melamine containing solid wastes are further processed or incinerated.
Shift workers are not exposed to melamine during routine production. Workers engaged in cleaning or filling or emergency operations may be exposed over some hours per week.
Source Agrolinz Melamin GmbH, Austria, 1998.

Remark: A dust loading in the working area of 1.14 mg/m^3 was determined in a processing plant at 36 °C and a wind speed of 4.2 m/s.
Source Agrolinz Melamin GmbH, Austria

Remark: Emission to air: < 100 kg/a at the production site (ca. 40 000 t/a) and < 50 kg/a at the processing site.
Source: BASF AG, Germany.

Remark: Discharge into atmosphere during manufacturing and further processing of the melamine produced in West Germany in 1989 is estimated at 850 kg, and into

waste water treatment plant of BASF AG, at 6 to 7 t. The contaminated residue (50 to 60 t/a) from production is landfilled as hazardous waste.
Source: (36)

Remark: Routes of exposure:
- via melamine-dust in handling and storage.
- contact with process streams with dissolved melamine/crystals.
Source: DSM Melamine, Netherlands.

Remark: 0.4 kg N is is released into the waste water per ton of melamine produced. < 0.02 kg Kj-nitrogen and 0 kg NO_3-nitrogen is released to the receiving river after degradation in the WWTP.
Production capacity of 180 000 t/a.
Source: DSM Melamine, Netherlands.

Remark: Fluidized bed reactor. Catalytic reaction : Al_2O_3 as catalyst. After reaction, melamin is obtained under gaseous form. Cristallization occurs at 170-180 °C.
Protective measures: gloves, goggles, glasses and anti-NH3 masks.
Source: Atochem, Paris.

Remark: There are ca. 43 000 employees at 2130 facilities that may be exposed to melamine (or melamine resins).
Source: OECD contact point in the USA.

1.10 Additional Remarks

Remark: Transport not restricted. Disposal according to local legislation.
Source: DSM Melamine, Netherlands.

2. PHYSICO-CHEMICAL DATA

2.1 Melting Point

Value: ca. 354 °C
Decomposition: at > 280 °C formation of NH_3.
Source: Agrolinz Melamin, Austria; DSM Melamine, Netherlands.

Value: ca. 350 degree C
Decomposition: yes
Sublimation: yes
Source: (33)

Value: /
Decomposition: yes
Remark: Dangerous decomposition products: NH_3 will be split off at > 300 °C and possibly HCN at > 600 °C which burns in the open flame.
Source: (33)

Value: 345 °C

Decomposition: yes
Source: (96)

2.2 Boiling Point

Value: /
Sublimation: yes
Source: (96)

2.3 Density

Type: density
Value: 1.574 g/cm^3 at 20 °C
Source: (33)

Type: bulk density
Value: ca. 300 - 600 kg/m^3
Method: DIN 53 468
Source: (33)

2.4 Vapour Pressure

Value: 4.7 x 10^{-8} Pa at 20 °C.
Method: Dynamic method with N_2 or NH_3 at 144 to 341 °C.
Extrapolation to 20 °C.
Result: log P(mm Hg) = 12.52 - [6440 / T(K)].
This is now transformed to log P(Pa) = 14.644 - [6440 / T(K)].
Year: 1960.
Remark: (4) presents another equation, also based on the same results of (67):
log P(10^5 Pa) = 9.7334 - [6484.9 / T(K)].
A vapour pressure of 4.1 x 10^{-8} Pa at 20 °C is calculated from this equation.
Source: (67)

Value: 50 mm Hg at 315 °C
Remark: This value is in agreement with the determinations made by (67). They found ca. 31 mm Hg at ca. 310 °C.
Source: (96)

2.5 Partition Coefficient

log Pow: -1.14 at 25 degree C
Method: OECD Guideline 107 "Partition Coefficient (n-octanol/water), Flask-shaking Method"
Year: 1988. GLP:
Test substance: 99.9 %.
Source: (30)

2.6 Water Solubility

Value: 3.2 g/l at 20 °C
pH: 7 - 8 at 3.2 g/l and 20 °C

Source: (33)

Value: 3 g/l at 20 °C
pH: typically 8.4 to 8.9 at 20 °C
Source: DSM Melamine, Netherlands

Value: < 1 g/l at 22 °C
Source: (96).

Value: /
Remark: The solubility L (in g / 100 g water) over the range of 20 - 100 °C is given by the equation: log L = 5.101 - 1642 / T.
L = 0.31 g / 100 ml (or 3.1 g/l) is calculated for 20 °C.
Year: 1943
Source: (37) cited in (4).

Ion formation:
Results: Melamine is a weak base. The basic ionisation constant Kb1 = 1 x 10-9 to 2.2 x 10-9 depending on the method used. The molecule is neutral in the pH range 6 to 13, it is simple protonated in the range 1 to 4 (another reported range is: 0.3 to 3).
Source: (57)

2.7 Flash Point

Not applicable as melamine is a solid.

2.8 Auto Flammability

Result: > 300 °C.
Source: Agrolinz Melamin GmbH, Austria.

Remark: Ignition temperature: > 600 °C
Source: (33)

2.9 Flammability

Result: non flammable
Method: Directive 84/449/EEC, A.10 "Flammability (solids)"
Year: 1987
Source: (33)

2.10 Explosive Properties

Result: not explosive
Method: Sprengstoffgesetz (German law on explosives)
Year: 1974
Source: (29)

Result: Weakly explosible - dust explosion class VDI 3673 St 1.
Method: VDI 3673

Year: 1990
Source: (43)

Result: Weakly explosible - dust explosion class 1.
Method: VDI 3673 ISO
Year: 1989
Source: (109)

2.11 Oxidizing Properties

Result: no oxidizing properties
Source: (29)

2.12 Oxidation reduction Potential

/.

2.13 Additional Remarks

Several thermodynamic data can be found in (4).

Solubility in other solvents:

DMSO	5-10 g/l, 22 °C
95 % Ethanol	< 1 g/l, 22 °C
Methanol	< 1 g/l, 19 °C
Acetone	< 1 g/l, 22 °C
Toluene	< 1 g/l, 20 °C
Benzene	insoluble
Ether	insoluble

Source: (96)

3. ENVIRONMENTAL FATE AND PATHWAYS

3.1.1 Photodegradation

Light spect. 235 nm
Method: other (measured)
Year: GLP:
Remark: Exctinction coefficient: 0.249 x 10^4 l/mol.cm; no absorption at > 310 nm.
Source: (119)

3.1.2 Stability in Water

Result: Melamine is hydrolysed in strong alkaline and acidic solutions. The rate constants at 100 °C are: k(s-1) = 3.80 x 10^{-6} [OH^-] respectively k(s-1) = 1.25 x 10^{-4} [H^+].
Remarks: No data for relevant environmental conditions are available.
Source: (57)

3.1.3 Stability in Soil

Method: other

Year: GLP:
Remark: Melamine is adsorbed to the soil only to a minor extent (soil adsorption coefficient = 53). It is degraded with a half life time of 2 - 3 years.
Year: 1983. GLP:
Source: (45)

Type: Degradation in soil.
Degradation:
Test condition: 2 soils, moderately aerated, 60% field capacity moisture, up to 28 weeks incubation at 32 °C.
Year: 1964. GLP:
Remark: 0 to 17.9 % triazine N nitrified in 6 - 24 weeks depending on the soil.
Source: (59)

3.2 Monitoring Data (Environment)

Remark: Concentrations were monitored in rivers of Japan. The production volume in Japan was 80 000 t in 1987.
Results 1986: Samples of water and sediment were taken at 10 different areas (mouth of rivers, channel, bays). Melamine was detected in 7 areas. Detected range in water: 0.0001-0.0016 ppm; detection limit: 0.0001 ppm. Detected range in bottom sediment: 0.088-0.13 ppm; detection limit: 0.07 ppm.
Results 1987: Samples of water, sediment and fish were taken at 50 different areas. Melamine was detected in 89/150 water samples in 33/50 areas; in 36/117 samples of bottom sediment in 18/40 areas and in 13/144 fish samples in 3/45 areas. Detected range in water: 0.0001-0.0076 ppm; detection limit: 0.0001 ppm. Detected range in bottom sediment: 0.01-0.32 ppm; detection limit: 0.01 ppm. Detected range in fish: 0.06-0.55 ppm; detection limit: 0.05 ppm.

High concentrations in the bottom sediment occured only in 2 samples from 1 area. Fish from lakes and marshes had the highest concentration.
Results 1988: Samples of fish were taken at 2 different areas. Melamine was detected in 9/12 fish samples in 1/2 areas. Detected range in fish: 0.09-0.23 ppm; detection limit: 0.05 ppm.
Results 1994: Samples of water, sediment and fish were taken. Melamine was detected in 43/150 water samples; in 29/160 samples of bottom sediment and in 12/148 fish samples.

Detected range in water: 0.00011-0.0064 ppm; detection limit: 0.00011 ppm. Detected range in bottom sediment: 0.015-0.40 ppm; detection limit: 0.015 ppm. Detected range in fish: 0.02-0.075 ppm; detection limit: 0.02 ppm.
Year: 1986-1994.
Reference: (12), (13), (100).

3.3 Transport and Distribution between Environmental Compartments

3.3.1 Transport

Type: Adsorption to soil
Result: Koc = 14.4

Method: calculated using the equation logKoc = 0.30 logKow + 1.50 given for triazines in (50)
Remark: Prefered data, because estimation is based on Pow (and not water solubility) and on a specific equation for this type of molecule.

Type: Adsorption to soil
Remark: Koc = 53 at 3000 mg / l. The result is estimated from water solubility.
Source: (45)

Type: Adsorption to soil
Remark: Calculated Koc = 51
Source: (124)

Type: volatility
Method: other
Year: 1988.
Remark: Henry-Constant =1.84 x 10^{-14} atm.m^3/mol = 1.8 x 10^{-9} Pa.m^3.mol^{-1} at 20 °C.
Source: (124)

3.3.2 Distribution

Method: Generic fugacity model, level 1. FUGMOD, Version 1.0, OECD 1992.
Results:

to air	0.000 000 04	%
to water	99.99	%
to soil solids	0.006	%
to sediment solids	0.000 1	%
to suspended sediment	0.000 004	%
to biota	0.000 000 4	%

3.4 Mode of Degradation in Actual Use

Degradation: Activated sludge of the waste water treatment plant (WWTP) of a melamine producer can rapidly degrade melamine. No melamine is detected anymore after 8 hours.
(No degradation was obtained with activated sludge of a community WWTP within 1 month.)
Method: ISO 7827:1984, but determination of melamine and not of the DOC.
Year: 1997. GLP: no.
Source: (54)

Type: Measurement in the waste water treatment plant of a melamine production plant.
Degradation: 80 to 90 % melamine is broken down.
Source: DSM Melamine, Netherlands.

3.5 Biodegradation

Type: aerobic
Inoculum: activated sludge
Concentration: 400 mg DOC/l
Degradation: 16 % after 20 day

Method: Zahn-Wellens test, OECD 302B of 1981.
Remark: The test was repeated with adapted inoculum. Result: elimination of 10 % after 14 days. Not easily degradable.
Year: 1991. GLP:
Source: (31)

Type: aerobic
Inoculum: activated sludge
Concentration: 100 mg DOC/l
Degradation: 0 % after 28 day
Method: Zahn-Wellens test, OECD 302B.
Year: 1993. GLP:
Test substance:
Source: (32)

Type: aerobic
Inoculum: activated sludge
Concentration: 100 mg melamine/l.
Degradation: 0 % after 14 day
Method: BOD. Concentration of sludge: 30 mg/l.
Year: < 1992. GLP:
Test substance:
Remark: The study is probably identical with the next entry (120)
Source: (2)

Type: aerobic
Inoculum: activated sludge
Degradation: < 30 % after 14 day
Method: other: ORIGINAL-MITI-Test, Biodegradability and Bioaccumulation Test of Chemical Substances (C-5/98/JAP) 1978.
Year: 1978 GLP:
Test substance:
Remark: 100 ppm test substance / 30 ppm sludge. BOD of the ThOD. Substance specific and unspecific chemical analyses.
Source: (120)

Type:
Inoculum: other bacteria: Pseudomonas sp. (various strains)
Degradation:
Method:
Year: 1981, 1982 GLP:
Test substance:
Remark: Melamine is degraded by Pseudomonas sp. (various strains) by desamination to cyanuric acid.
Source: (40), (75)

3.6 BOD5, COD and BOD5/COD Ratio

Type: aerobic
Inoculum:
Degradation: 0 %

Method:
Year: 1955 GLP:
Test substance:
Remark: BOD5 = 0% BODTh at 20 deg C; no degradation.
Source: (66)

Type:
Inoculum: other bacteria: adapted inoculum
Degradation: < 1 % after 5 day
Method: BSB-Test (BOD of the ThOD).
Year: 1987 GLP:
Test substance:
Remark: In addition: BOD5 of the ThOD = 1 % (inoculum is unknown). BOD5 of the ThOD = 0 % with adapted inoculum.
Source: (94)

Type:
Inoculum: sewage effluent
Degradation: practically no BOD in 5 days.
Method:
Year: 1950 GLP:
Test substance:
Remark:
Source: (126)

3.7 Bioaccumulation

Species: Cyprinus carpio
Exposure period: 42 days at 25 °C
Concentration: 0.2 and 2 mg/l
BCF: < 0.38 for 2 mg/l and < 3.8 for 0.2 mg/l.
Elimination:
Method: OECD 305C, Bioaccumalation: test for the degree of bioconcentration in fish.
Year: < 1992 GLP:
Test substance:
Source: (2)

Species: /
Exposure period:
Concentration:
BCF: ca. 15
Elimination:
Method: calculated according to Chiou,C.T. et al., Environ. Science & Technol. 11(5), 475-478, (1977).
Year: GLP:
Test substance:
Remark: No remarkable bioaccumulation is expected from the log Pow of -1.14 and the calculted BCF.
Source: (45)

3.8 Additional Remarks

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4. ECOTOXICITY

4.1 Acute and Prolonged Toxicity to Fish

Type:
Species: Leuciscus idus melanotus (Fish, fresh water)
Exposure period: 48 hour
Unit: mg/l
Analytical monitoring:
LC50: > 500
Method: DIN 38 412 L-20.
Year: 1989. GLP:
Test substance:
Source: (42)
Type:
Species: Oryzias latipes (Fish, fresh water)
Exposure period: 48 hour
Unit: mg/l
Analytical monitoring:
LC50: 1000
Method: Modified MITI Test (II) stipulated in the OECD guidelines.
Year: < 1992. GLP:
Test substance:
Source: (2)

Type:
Species: Poecilia reticulata (Fish, fresh water)
Exposure period: 96 hour
Unit: mg/l
Analytical monitoring:
LC50: > 3000
Method:
Year: 1991. GLP:
Test substance:
Source: (93)

Type:
Species: Poecilia reticulata (Fish, fresh water)
Exposure period: 96 hour
Unit: mg/l
Analytical monitoring:
Method:
Year: 1978. GLP:
Test substance:
Remark: 4400 mg/l were lethal to < 10 % of the animals.
Source: (73)

4.2 Acute Toxicity to Aquatic Invertebrates (e.g. Daphnia)

Species: Daphnia magna (Crustacea)
Exposure period: 48 hour
Unit: mg/l
Analytical monitoring:
EC50: > 2000
Method: Acute toxicity test.
Year: 1978. GLP:
Test substance:
Source: (1)

4.3 Toxicity to Aquatic Plants (e.g. Algae)

Species: Scenedesmus pannonicus (Algae)
Endpoint: growth
Exposure period: 4 day
Unit: mg/l
Analytical monitoring:
NOEC: 320
EC50: 940
Method: Growth inhibition test.
Year: 1982 GLP:
Test substance:
Source: (17)

4.4 Toxicity to Microorganisms (e.g. Bacteria)

Type: Inhibition of activated sludge
Exposure period: 30 min
Unit: mg/l
EC0: > 1992
Method: OECD 209; EC88/302, ISO 8192. Test for Inhibition of Oxygen Consumption by Activated Sludge.
Year: 1991 GLP:
Test substance:
Source: (31)

Type:
Species: Nitrosomonas sp. (Bacteria)
Exposure period: 2 hour
Unit: mg/l
Analytical monitoring:
EC0: > 100
Method: Inhibition of the ammonium oxidation.
Year: 1977 GLP:
Test substance:
Source: (68)

Type:
Species: Pseudomonas putida (Bacteria)

Exposure period: 30 minutes
Unit: mg/l
Analytical monitoring:
EC10: > 10000
EC50: > 10000
Method: Pseudomonas respiration inhibition test, DIN 38412, Part 27, draft.
Year: 1990 GLP:
Test substance:
Source: (34)

4.5 Chronic Toxicity to Aquatic Organisms

4.5.1 Chronic Toxicity to Fish

Species: Jordanella floridae (Fish, fresh water)
Endpoint: Egg-larval development, hatchability, toxicity to fish larvae until 28 days after hatching.
Exposure period: 35 day
Unit: mg/l
Analytical monitoring:
NOEC: ≥ 1000
Method:
Year: 1982 GLP:
Test substance:
Source: (23)

Species: Salmo gairdneri
Endpoint: Larval and post-larval development.
Exposure period:
Unit: mg/l
Analytical monitoring:
$NOEC_{macroscop.}$: 500
$NOEC_{microscop.}$: < 125
Method: Flow through system. Histological examination of the embryos.
Year: 1982 GLP:
Test substance:
Results: Histological examination of hatching embryos exposed at 125 mg/l revealed increased alterations in the epidermis, pronephros and neural tube. Malformations were macroscopically visible at 1030 mg/l.
Source: (110)

4.5.2 Chronic Toxicity to Aquatic Invertebrates (e.g. Daphnia)

Species: Daphnia magna
Endpoint: Mortality, reproduction.
Exposure period: 21 day
Unit: mg/l
Analytical monitoring:
NOEC: 18
LC100 : 56
Method: Chronic toxicity and reproduction test

Year: 1978 GLP:
Test substance:
Remark: 32 mg/l < $LC50_{21d}$ < 56 mg/l.
No effect to reproduction (tested up to 32 mg/l).
Source: (1)

4.6 Toxicity to Terrestrial Organisms

4.6.1 Toxicity to Soil Dwelling Organisms

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4.6.2 Toxicity to Terrestrial Plants

Species: Hordeum vulgare
Endpoint: growth
Exposure period: 4 day
Unit: mg/l
EC50: 530
Method:
Year: 1992 GLP:
Test substance:
Remark: Root growth reduction, melamine in soil percolate.
Source: (77)

Species: Tritium aestivum (Monocotyledon)
Endpoint: growth
Exposure period: 4 day
Unit: mg/l
EC50: 900
Method:
Year: 1992 GLP:
Test substance:
Remark: Root growth reduction, melamine in soil percolate.
Source: (77)

Species: Raphanus sativus (Dicotyledon)
Endpoint: growth
Exposure period: 4 day
Unit: mg/l
EC50: 930
Method:
Year: 1992 GLP:
Test substance:
Remark: Root growth reduction, melamine in soil percolate.
Source: (77)

Species: Lepidum sativum (Dicotyledon)
Endpoint: growth
Exposure period: 4 day
Unit: mg/l
EC50: 1100

Method:
Year: 1992 GLP:
Test substance:
Remark: Root growth reduction, melamine in soil percolate.
Source: (77)

Species: other terrestrial plant: Pisum sativum/Phaseolus vulgaris
Endpoint: growth, germination
Exposure period: 14 day
Unit: ppm
NOEC: 1680
Method:
Year: 1992 GLP:
Test substance:
Source: (74)

4.6.3 Toxicity to Other Non-mammalian Terrestrial Organisms

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4.7 Biological Effects Monitoring

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4.8 Biotransformation and Kinetics Excluding Mammals

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4.9 Additional Remarks

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5. TOXICITY

5.1 Acute Toxicity

5.1.1 Acute Oral Toxicity

Type: LD50
Species: rat, F344
Value: males: 3161 mg/kg bw
females: 3828 mg/kg bw
Method:
Year: 1983. GLP: NTP-Standard
Test substance:
Remark: gavage, corn oil as vehicle.
Source: (11)

Type: LD50
Species: mouse, B6C3F1
Value: males: 3296 mg/kg bw
females: 7014 mg/kg bw
Method:
Year: 1983. GLP: NTP-Standard

Test substance:
Remark: gavage, corn oil as vehicle.
Source: (11)

Type: LD50
Species: rat
Value: > 6400 mg/kg bw
Method: other: BASF-test
Year: 1969. GLP: no
Test substance:
Remark: suspension in traganth.
Source: (29)

Type: LD50
Species: mouse
Value: 4550 mg/kg bw
Method:
Year: 1955. GLP:
Test substance:
Source: (25)

5.1.2 Acute Inhalation Toxicity

Type: Inhalation risk test
Species: rat
Exposure time: 8 hours
Value:
Method: BASF-test
Year: 1969. GLP: no
Test substance:
Remark: Inhalation of saturated vapour (20 °C) killed 0/12 rats.
Source: (29)

Type: LC50
Species: rat
Exposure time:
Value: 3.248 mg/l
Method: no data
Year: 1993. GLP: no data
Source: (132)

5.1.3 Acute Dermal Toxicity

Type: LD50
Species: rabbit
Route of admin.: dermal
Value: > 1000 mg/kg bw
Method:
Year: < 1990. GLP:
Test substance:
Source: (21)

5.1.4 Acute Toxicity, Other Routes

Type: LD50
Species: mouse
Route of admin.: i.p.
Value: = 112 mg/kg bw
Method:
Year: 1977. GLP:
Test substance:
Source: (118)

Type: LD50
Species: mouse
Route of admin.: i.p.
Value: = 800 mg/kg bw
Method: BASF-test
Year: 1969. GLP: no
Test substance:
Source: (29)

5.2 Corrosiveness and Irritation

5.2.1 Skin Irritation

Species: rabbit
Result: not irritant
Method: OECD No. 404.
Year: 1995. GLP: yes.
Source: (112)

Species: rabbit
Result: not irritating
Method: BASF-Test
Year: 1969. GLP: no
Source: (29)

Species: rabbit
Result: not irritating
Year: 1955. GLP:
Remark: 1 g aqueous paste / kg bw and also 0.1 g of a 4 % aqueous solution / kg bw, occlusive, 18 h.
Source: (25)

Species: guinea pig
Result: not irritating
Year: GLP:
Test substance: 1% melamine solution in water
Source: (51)

5.2.2 Eye Irritation

Species: rabbit

Result: not irritating
Method: BASF-Test
Year: 1969. GLP: no
Source: (29)

Species: rabbit
Result: not irritating
Year: 1955. GLP:
Remark: 0.05 ml of a 10 % suspension were dosed.
Source: (25)

Species: rabbit
Result: not irritating
Year: 1955. GLP:
Remark: 30 mg dry powder were dosed; observed effects were characterized as mild.
Source: (25)

5.3 Sensitization

Type: Patch-Test
Species: human
Result: not sensitizing
Classification:
Method:
Year: 1955. GLP:
Test substance:
Source: (25)

Type:
Species: guinea pig
Result: not sensitizing
Classification:
Method:
Year: < 1963 GLP:
Test substance:
Remark: not a sensitizer; original source not available.
Source: (51)

5.4 Repeated Dose Toxicity

5.4.1 Repeated Oral Dose Toxicity with Rats

Species: rat
Sex: male/female
Strain: Fischer 344
Route of admin.: oral feed
Exposure period: 14 days
Frequency of treatment: continuously
Post. obs. period: none
Doses: 5000; 10000; 15000; 20000; 30000 ppm (417-2500 mg/kg)
Control Group: concurrent, no treatment

NOAEL: 5000 ppm
Method:
Year: 1983
GLP: NTP-Standard
Test substance: ca. 3 % impurities.
Remark: NOEL: 5000 ppm (m); 10000 ppm (f)
Result: All animals survived to the end of the dosing period. All female and male rats receiving 15000 ppm and more had mean body weight gain depressions when compared to the controls. Male and female rats receiving 20000 or 30000 ppm melamine lost weight. Hard crystalline solids were found in the urinary bladder of 4/5 to 5/5 male rats in groups fed 10000 ppm or more and 4/5 female rats in groups fed 20000 ppm or more. The kidneys of 2 males in the high dose group were pale and pitted. Apart from urinary tract no compound-related effects were observed in other organs.
Source: (97)

Species: rat
Sex: male/female
Strain: Fischer 344
Route of admin.: oral feed
Exposure period: 28 days
Frequency of treatment: continuously
Post. obs. period:
Doses: 480 to 4280 ppm (corresponding doses: up to 357 mg/kg)
Control Group:
Method:
Year: 1984
GLP:
Test substance:
Result: Incidence and size of bladder stones were directly related to the amount of substance administered. The larger stones were found to be unchanged melamine in a matrix of protein, uric acid and phosphate.
Remark: Only a very short summary is cited.
Source: (24)

Species: rat
Sex: male
Strain: Fischer 344
Route of admin.: oral feed
Exposure period: 4 weeks
Frequency of treatment: continously
Post. obs. period: none
Doses: 2000; 4000; 7000; 10000; 13000; 16000; 19000 ppm (corresponding dose: 133 - 1267 mg/kg)
Control Group: concurrent, no treatment
NOAEL: 2000 ppm for calculi formation.
Method:
Year: 1982.
GLP: yes
Test substance:

Result: The study was conducted in order to evaluate urolithiasis induction by melamine. In-life observations indicated a significant dose-related depression in body weight gain, elevated water intake and altered food consumption pattern. In addition, melamine produced a dose-dependent incidence of urinary bladder calculi and urinary bladder hyperplasia. All animals (40 per group) with hyperplasia, except one, had calculi. Spectroscopic analysis of stones indicated the presence of melamine, phosphorus, sulfur, potassium and chloride. Urinalysis demonstrated dose-dependent trends to aciduria and crystalluria. A second part of the report describes in detail analysis of plasma, urine and calculi.
Source: (19)

Species: rat
Sex: male/female
Strain: Fischer 344
Route of admin.: oral feed
Exposure period: 13 weeks
Frequency of treatment: continuously
Post. obs. period: none
Doses: 750; 1500; 3000; 6000; 12000 ppm (63 - 1000 mg/kg)
Control Group: concurrent, no treatment
NOEL: ≤ 63 mg/kg bw
Method:
Year: 1983
GLP: NTP-Standard
Test substance: ca. 3 % impurities.
Result: Body weight gain was depressed in males receiving 6000 and 12000 ppm but not in females. Food consumption was not affected. Urinary bladder stones occurred in all the treated male rats in a dose-related manner (control: 1/10; 750 ppm: 2/10; 12000 ppm: 9/9). Hyperplastic epithelial changes were only found in males. Dose-related calcerous deposits were observed in the proximal tubules in the kidney of female rats.
Source: (11), (97)

Species: rat
Sex: male/female
Strain: Fischer 344
Route of admin.: oral feed
Exposure period: 13 weeks
Frequency of treatment: continuously
Post. obs. period: none
Doses: 6000; 9000; 12000; 15000; 18000 ppm; (corresponding daily intake: ca. 500-1500 mg/kg)
Control Group: concurrent, no treatment
Method:
Year: 1983
GLP: NTP-Standard
Test substance: ca. 3 % impurities.
Result: One male rat receiving 18000 ppm and two males receiving 6000 ppm died. Body weight gain was depressed in males and females receiving 12000 ppm or more. Food consumption was reduced in the high dose group. Urinary

bladder stones occurred in males of all treated groups (dose-related) and in female rats of the two highest dose groups. Histopathology was performed in the high and low dose group. Diffuse epithelial hyperplasia of the urinary bladder was found in 8/10 males and 2/10 females in the 18000 ppm group. Only 1/10 males receiving 6000 ppm had hyperplastic changes of the urinary bladder.

Source: (11), (97)

Species: rat
Sex: male/female
Strain: Fischer 344
Route of admin.: oral feed
Exposure period: 13 weeks
Frequency of treatment: continuously
Post. obs. period: none
Doses: 10000; 18000 ppm (corresponding doses 833; 1500 mg/kg)
Control Group: concurrent, no treatment
Method: Ammonium chloride was added to the drinking water in some groups to investigate if such treatment might affect the incidence of stone formation in the urinary tract.
Year: 1983
GLP: NTP-Standard
Test substance:
Result: There was no difference between groups receiving melamine with or without ammonium chloride.
Source: (97)

5.4.2 Repeated Dose Toxicity with Other Species or Other Routes

Species: rat
Sex: male/female
Strain: Wistar
Route of admin.: i.p.
Exposure period: 5 days
Frequency of treatment: daily
Post. obs. period:
Doses: 500 mg/kg
Control Group: concurrent, no treatment
Method:
Year: 1950.
GLP:
Test substance:
Result: There was a moderate weight loss. In two animals crystalline deposits were found in renal tubules. The toxic effects of several S-Triazines with Nitrogen-Mustard like action were compared to the effects of melamine. Melamine did not induce Nitrogen-Mustard like actions on peripheral blood or bone marrow. No intestinal lesions could be found in animals treated with melamine. Also mice tolerated five successive daily doses of melamine (500 mg/kg; i.p.). No further results are presented.
Source: (108)

Species: mouse
Sex: male/female
Strain: B6C3F1
Route of admin.: oral feed
Exposure period: 14 days
Frequency of treatment: continuously
Post. obs. period: none
Doses: 5000; 7500; 10000; 12500; 15000; 30000 ppm (1000-6000 mg/kg)
Control Group: concurrent, no treatment
NOAEL: 15000 ppm
Method:
Year: 1983
GLP: NTP-Standard
Test substance: ca. 3 % impurities.
Result: 2/5 female and all the male mice in the high dose group had urinary bladder stones. No other compound-related effects were noted.
Source: (97)

Species: mouse
Sex: male/female
Strain: B6C3F1
Route of admin.: oral feed
Exposure period: 13 weeks
Frequency of treatment: continuously
Post. obs. period: none
Doses: 6000; 9000; 12000; 15000; 18000 ppm; (m: 1600-4800; f: 2400-7200 mg/kg bw.day)
Control Group: concurrent, no treatment
Method:
NOEL: 6000 ppm.
Year: 1983
GLP: NTP-Standard
Test substance: ca. 3 % impurities.
Result: Mean body weights were lower in treated animals compared to controls. However the effects were not dose-related. The incidence of mice bearing bladder stones (occurred in all treated groups) appeared to be dose-related. Ulceration of the urinary bladder was observed in males fed diets containing 9000 ppm or higher and in females fed 15000 ppm or higher. Epithelial hyperplasia or atypical epithelial cells were seen in the males of the high dose and 9000 ppm group respectivly. Sixty per cent of the mice having bladder ulcers had urinary bladder stones as well. One female mouse receiving 9000 ppm died.
Source: (11), (97)

Species: rabbit
Sex: male
Strain:
Route of admin.: oral feed
Exposure period: one to four weeks
Frequency of treatment: daily
Post. obs. period:

Doses: 1 mM/kg (126 mg/kg)
Control Group:
Method:
Year: 1945.
GLP:
Test substance:
Result: There were no clinical, pathological or histological findings. Conduction and reporting of the study is insufficient compared to current standards.
Source: (80)

Species: dog
Sex: female
Strain:
Route of admin.: oral feed
Exposure period: one to four weeks
Frequency of treatment: daily
Post. obs. period:
Doses: 1 mM/kg (126 mg/kg)
Control Group:
Method:
Year: 1945.
GLP:
Test substance:
Result: No signs of toxicity or gross and microscopical changes were seen. Conduction and reporting of the experiment is insufficient compared to current standards.
Source: (80)

Species: dog
Sex:
Strain:
Route of admin.: oral feed
Exposure period: 1 year
Frequency of treatment: continuously
Post. obs. period:
Doses: 30000 ppm (corresponding dose: 1200 mg/kg)
Control Group: concurrent, no treatment
Method:
Year: 1955
GLP:
Test substance:
Result: Apart from crystalluria which started after 60 to 90 days and persisted during the study period no other effects attributable to melamine feeding were observed.
Source: (25)

5.5 Genetic Toxicity in vitro

A. Bacterial Tests

Type: Ames test

System of testing: Salmonella typhimurium, TA100, TA98, TA97 and TA102.
Concentration: up to 5000 µg/plate
Metabolic activation: with and without S9
Result: negative
Method: Matsushima T. et al., Short term test systems for detecting carcinogens, Springer Verlag, 1980.
Year: 1991. GLP:
Test substance:
Remark:
Source: (70)

Type: Ames test
System of testing: Salmonella typhimurium, TA98, TA100, TA1535, TA1538.
Concentration:
Metabolic activation: with and without S9
Result: negative
Method:
Year: 1991. GLP:
Test substance:
Remark: Comparison of mutagenic properties of 17 S-Triazine Compounds in Salmonella. Only triethylenemelamine (TEM) was active.
Source: (84)

Type: Ames test
System of testing: Salmonella typhimurium; TA98, TA100, TA1535, TA1537.
Concentration: up to 1111 µg/plate
Metabolic activation: with and without S9
Result: negative
Method:
Year: 1983. GLP:
Test substance:
Source: (60)

Type: Ames test
System of testing: Salmonella typhimurium; TA98, TA100, TA1535, TA1537, TA1538.
Concentration: 50 - 5000 µg/plate
Metabolic activation: with and without S9 mix
Result: negative
Year: 1981. GLP: yes
Test substance:
Remark: plate incorporation assay
Source: (26)

Type: Ames test
System of testing: Salmonella typhimurium; TA98, TA100, TA1535, TA1537, TA1538.
Concentration: 0.1 - 500 µg/plate
Metabolic activation: with and without S9
Result: negative
Method:
Year: 1977. GLP:

Test substance:
Source: (81)

Type: Ames test
System of testing: Salmonella typhimurium hisG 46; TA1530, TA1531, TA1532, TA1534.
Concentration:
Metabolic activation:
Result: negative
Method:
Year: 1973. GLP:
Test substance:
Source: (121)

Type: DNA damage and repair assay
System of testing: E.coli WP2uvrA, W3110/polA+, p3478/polA-.
Concentration: 0.1 - 500 µg/plate
Metabolic activation: with and without S9
Result: negative
Method:
Year: 1977. GLP:
Test substance:
Source: (81)

Type: Bioluminescence Assay (Mutatox (TM))
System of testing: Photobacterium phosphoreum dark mutation
Concentration: no data
Metabolic activation: no data
Result: negative
Method: The ability of test chemicals to restore luminescence of Photobacterium phosphoreum is assessed. The repression of the luminescence operon is believed to be the cause of the mutant phenotype. Besides detecting genotoxic agents, the assay may give positive results for protein cross-linkers and for agents that alter gene expression, because targets of the active compound include both protein (e.g. the repressor) and DNA-sites (e.g. luciferase genebinding site).
Year: 1990. GLP:
Test substance:
Remark: Compared to the Ames test, the sensitivity, specificity and accuracy of the Mutatox Assay for predicting carcinogenicity of 66 chemicals was lower.
Source: (46)

Type: Microscreen Assay (lambda prophage induction)
System of testing: E. coli strain WP2s (lambda)
Concentration: serial dilutions.
Metabolic activation: with and without.
Result: positive.
Method: The assay is an indicator for DNA damage. It measures the induction of lambda prophage in E. coli, which results from derepression of the bacterial SOS system, a set of coordinately regulated genes that become activated when DNA is damaged. Upon SOS-activation, the prophage is excised from

E. coli genome and thus enters into the lytic pathway (multiple replication of viral DNA, packaging, lysis of the host cell and release of lambda virions).
Year: 1991. GLP:
Test substance:
Remark: Maximum enhancement of lambda prophage induction was observed at melamine concentrations of 312 µg/ml. In the absence of S9-activation, lambda prophage induction was enhanced by factor 7 over background, while enhancement was 4 times in the presence of S9 mix.
Source: (114)

B. Non-Bacterial in vitro Tests

Type: Point mutation
System of testing: Saccharomyces cerevisiae D4
Concentration:
Metabolic activation: with and without S9
Result: negative
Method:
Year: 1977. GLP:
Test substance:
Source: (82)

Type: HGPRT forward mutation assay
System of testing: CHO cells
Concentration: 600 - 1000 µg/ml
Metabolic activation: with and without S9
Result: negative
Method:
Year: 1982. GLP:
Test substance:
Source: (87)

Type: Mouse lymphoma assay
System of testing: Mouse lymphoma cells L5178Y
Concentration:
Metabolic activation:
Result: negative
Method:
Year: 1986. GLP:
Test substance:
Remark: Results presented in schedule. Probably identical with source (89).
Source: (95)

Type: Mouse lymphoma forward mutation assay
System of testing: Mouse lymphoma cells L5178Y tk^+/tk^-
Concentration: up to 160 µg/ml
Metabolic activation: with and without S9
Result: negative
Method:
Year: 1988. GLP:
Test substance:

Source: (89)

Type: Cytogenetic assay
System of testing: CHO cells
Concentration: 240 - 300 µg/ml
Metabolic activation: with and without S9
Result: negative
Method:
Year: 1987. GLP:
Test substance:
Source: (56)

Type: Sister chromatid exchange assay
System of testing: CHO cells
Concentration: 150 - 300 µg/ml
Metabolic activation: with and without S9
Result: equivocal; there was a small significant increase of SCE without S9 in one of two trials. The tests with S9 were negative.
Method:
Year: 1987. GLP:
Test substance:
Source: (56)

Type: Sister chromatid exchange assay
System of testing: CHO cells
Concentration: 0.63 - 630 µg/ml
Metabolic activation: with and without
Result: negative
Method:
Year: 1982. GLP: yes
Test substance:
Source: (28), (87)

Type: Unscheduled DNA synthesis
System of testing: Rat hepatocytes
Concentration:
Metabolic activation:
Result: negative
Method:
Year: 1983. GLP:
Test substance:
Source: (91)

Type: DNA damage and repair assay
System of testing: Rat Hepatocyte Primary Culture
Concentration: 0.06 - 6 mg/ml
Metabolic activation:
Result: negative
Method:
Year: 1982. GLP: yes

Test substance:
Remark: DNA-Repair Test
Source: (27)

Type: DNA synthesis-inhibition test
System of testing: HeLa S3 cells
Concentration:
Metabolic activation: unclear
Result: negative
Method: Heil J. et al., Anal. Biochem. 187, 314-317, 1990.
Year: 1992. GLP:
Test substance:
Remark: The test is proposed as an indicator test for mammalian genotoxicity, based on the observation that binding of chemical carcinogens to DNA initially inhibits its replication. This in turn appears to lead to an accumulation of DNA strand breaks, DNA adducts, chromosome aberrations and mutations, all of which predispose to an increased cancer rate. The concentration which inhibits DNA synthesis by 50 % was > 300 µM.
Source: (63)

Type: Cell transformation assay
System of testing: Balb/c 3T3
Concentration:
Metabolic activation: with and without rat hepatocytes
Result: negative
Method:
Year: 1986. GLP: NTP-Standard
Test substance:
Remark: A survey of the genotoxicity test results generated by the NTP is given: TA100,1535,1537, 98: negative without and with S9.
Cytogenetic aberrations in vitro: negative without and with S9.
SCE invitro: negative without and with S9.
UDS in vitro: negative.
Source: (128)

5.6 Genetic Toxicity in vivo

Type: Micronucleus assay
Species: mouse
Sex: male/female
Strain: CD-1
Route of admin.: oral, gavage
Exposure period: single application and also 2 doses separated by 24 h.
Doses: 1000 mg/kg
Method: Animals were sacrificed 30 and 48 h p.a. In the second experiment mice were sacrificed 48 and 72 h after the first application.
Year: 1981. GLP: yes
Test substance:
Result: Negative.
Source: (107), (86)

Type: Micronucleus assay
Species: mouse
Sex: male
Strain: B6C3F1
Route of admin.: i.p.
Exposure period: 1 injection per day on 3 consecutive days
Doses: 0, 500, 1000, 2000 mg/kg
Method:
Year: 1993. GLP:
Test substance:
Result: Negative.
The initial test gave a positive trend from 2.1 micronucleated polychromatic erythrocytes / 1000 to 3.8 in the high dose. Peripheral blood smears were negative as was a repeat bone marrow test using doses of 1000 and 2000 mg/kg bw/day.
Source: (122)

Type: Drosophila SLRL test
Species: Drosophila melanogaster
Sex: male
Strain:
Route of admin.: oral, feed
Exposure period: 3 days
Doses: 0.023%; 1% solution
Method:
Year: 1963. GLP:
Test substance:
Result: negative
Source: (83)

5.7 Carcinogenicity

Species: rat
Sex: male/female
Strain: Fischer 344
Route of admin.: oral feed
Exposure period: 105 weeks
Frequency of treatment: continuously
Post. obs. period: none
Doses: m: 2250; 4500 ppm (ca. 126; 263 mg/kg bw)
f: 4500; 9000 ppm (ca. 262; 542 mg/kg bw)
Control Group: concurrent, no treatment
Method:
Year: 1983
GLP: NTP-Standard
Test substance: ca. 3 % impurities.
Result: Survival of high dose male rats was significantly reduced (38%) compared to the controls (61%). The incidence of transitional- cell carcinomas was significantly increased (8/49) compared to the controls (0/49). In that high dose male group one additional transitional-cell papilloma could be found. Ten animals had bladder stones. There was a significant correlation between

bladder stones and bladder tumors. 7 out of 8 animals with bladder carcinoma showed macroscopic bladder sediments. There was an increased incidence of chronic inflammation of the bladder only in the treated female rats. One female rat of the high and one of the low dose group had a transitional-cell papilloma of the bladder as well.

Source: (11)

Species: mouse
Sex: male/female
Strain: B6C3F1
Route of admin.: oral feed
Exposure period: 105 weeks
Frequency of treatment: continuously
Post. obs. period: none
Doses: 2250; 4500 ppm (m: ca. 327; 688 mg/kg bw. f: ca. 523; 1065 mg/kg bw)
Control Group: concurrent, no treatment
Method:
Year: 1983
GLP: NTP-Standard
Test substance: ca. 3 % impurities.
Result: Survival of high dose male mice was significantly reduced. In treated male mice there was an increased incidence of urinary bladder stones, and of acute and chronic inflammation and epithelial hyperplasia of the urinary bladder. There were no other lesions associated with the administration of melamine.
Source: (11)

Species: rat
Sex: male/female
Strain: Fischer 344
Route of admin.: oral feed
Exposure period: 24 to 30 months
Frequency of treatment: continuously
Post. obs. period: none
Doses: 100; 500; 1000 ppm (males); 100; 1000; 2000 ppm (females); (corresponding daily intake: up to 133 mg/kg)
Control Group: concurrent, no treatment
Method:
Year: 1983
GLP: yes
Test substance:
Result: Haematological, clinical investigations and urinalysis failed to show any difference between treated and controls except a dose-related trend for dilated glands in glandular gastric mucosa and inflammation in non glandular gastric mucosa. Urinary bladder calculi formation was not observed in this study. A total of 4 tumors of the urinary bladder were observed (two in controls, one in 1000 ppm male, one in 500 ppm female). The tumors were not accompanied by other lesions of the urinary bladder wall or cystic calculi. The study was conducted in order to clarify effects observed in the NTP carcinogenesis study (11), (97) in F-344 rats.
Source: (6)

Species: rat
Sex: male/female
Strain:
Route of admin.: oral feed
Exposure period: 2 years
Frequency of treatment: continuously
Post. obs. period:
Doses: 1000; 10000 ppm (corresponding doses 67; 667 mg/kg)
Control Group: concurrent, no treatment
Method:
Year: 1953
GLP:
Test substance:
Result: At the 1000 ppm level general health (food consumption, growth rate, nutrition, mortality) was not significantly different from controls. At the 10000 ppm level there was an increase in the incidence of urinary bladder stones (6/20) and associated an increase of benign papillomata. No other health effects were observed. NOEL = 1000 ppm.
Source: (25)

Species: rat
Sex: male
Strain: Fischer 344
Route of admin.: oral, feed
Exposure period: 36 weeks
Frequency of treatment: continously
Post. obs. period: 0-4 weeks
Doses: 3000, 10000, 30000 ppm (ca. 110, 367, 1100 mg/kg/d)
Control Group: concurrent, no treatment
Method: Urinary bladder lesions induced by thymine or melamine were investigated.
Year: 1992
GLP:
Test substance: > 99 %.
Result: Haematuria and polyuria were found with rats fed 3 % melamine for 36 weeks. In rats of this group, water intake was markedly increased, while food consumption and body weight gain was decreased compared to controls. Relative bladder weights were significantly increased in rats of the mid- and high-dosed group; in the latter group, the absolute bladder weight was significantly elevated over controls and a remarkable distension of the bladder was observed.
Exploratory laparatomy performed at the end of week 36 revealed calculus formation in 7/10 mid- and 10/10 high-dose rats. Calculi formation was significantly correlated with the incidence of bladder tumors. Carcinomas of the urinary bladder were observed in 1/20 rats fed 1 % melamine, and in 15/19 rats given 3 % melamine in the diet; papillomas were induced in 1/20 and 12/19 rats, respectivly.
In the high dose group, papillomas were also found in the ureter of 3 rats; in the ureter of 1 rat, a carcinoma was induced. Papillary / nodulary hyperplasia of the bladder epithelium was observed in 1 of 20 rats treated with 0.3 % melamine, while in rats fed 1 or 3 % melamine, the incidences were 6/20 or 12 /19, respectivly.

Remark: Also thymine at high concentration caused bladder calculi, papillomas and 1 carcinoma.
Source: (16)

Species: rat
Sex: male
Strain: Fischer 344/DuCrj
Route of admin.: oral, feed
Exposure period: 36 weeks
Frequency of treatment: continously
Post. obs. period: 4 weeks
Doses: 10000, 30000 ppm (ca. 430, 1200 mg/kg/d)
Control Group: concurrent, no treatment
Method: 8 groups of rats received diets containing 1 or 3 % melamine alone or in combination with either 5 or 10 % NaCl, or 10 % NaCl alone for 36 weeks, followed by basal diet for 4 weeks. Control rats received basal diet throughout the entire study period. NaCl was added to induce polyuria, by thus prevent calculi formation, and to allow assessment of the relationship between uroliths and lesion development.
Year: 1995
GLP:
Test substance: 99.9 % purity.
Result: Spontaneous deaths were limited to 3 rats with 1 % melamine who died during the treatment period. Body weight gains were lower in rats of treatment groups. The final body weight in the group treated with 3 % melamine alone were particularly low; average daily food consumption was slightly decreased in this group. The water intake taken to reflect urinary volume, was increased by NaCl treatment.
The incidence of bladder transitional cell carcinomas and papillomas were
90 and 55 % in the group treated with 3 % melamine alone;
90 and 25 % in the group treated with 3 % melamine and 5 % NaCl;
0 and 15 % in the group treated with 3 % melamine and 10 % NaCl;
21 and 42 % in the group treated with 1 % melamine alone; and
0 % in the other groups.
Calculus formation resulting from 1 % melamine treatment was suppressed dose-dependently by simultaneous NaCl treatment. The incidence of hyperplasia of the papilla and ischemic changes in the kidneys were dose-dependently suppressed by the addition of NaCl.
The main constituents of the calculi were melamine itself and uric acid. The results indicate that melamine-induced proliferative lesions of the rat urinary tract were directly due to the irritative stimulation of calculi, and not to molecular interactions between melamine itself or its metabolites with the bladder epithelium.
Source: (15)

Species: mouse
Sex: female
Strain: CD-1
Route of admin.: dermal
Exposure period: single application
Frequency of treatment: single application

Post. obs. period: 31 weeks
Doses: 1 µmol
Control Group: Acetone + TPA. Positive control: Triethylenemelamine.
Method:
Year: 1983
GLP:
Test substance:
Result: An initiation-promotion experiment with a single painting of melamine followed by a promotional treatment (two applications of TPA per week, for a period of 31 weeks) was performed in mouse skin. The incidence of papillomas after 31 weeks was 14% in the acetone controls, 19% in the group which received melamine and 75% in the group given triethylenemelamine. In contrast to triethylenemelamine melamine did not act as an initiating agent in mouse skin.
Source: (18)

Type of study: Evaluation
Year: 1984
Result: When evaluating the results from subchronic and chronic feeding studies with melamine, especially the NTP carcinogenesis assay (11) and the American Cyanamid Corporation carcinogenesis assay (6), the FDA Cancer Assessment Committee found that melamine is only indirectly responsible for bladder tumors, in that stones occurred only at high melamine doses and it is the stones, not melamine, that are tumorigenic. A synopsis of the group's findings follows:
1. There is a direct correlation between the occurence of bladder neoplasm and the formation of calculi in the same bladder. Since bladder calculi have been considered in previous studies to be associated with the formation of bladder neoplasms in rats, "their presence completely obfuscates any plausible case which might be made for a treatment-related chemical induction of bladder neoplasms".
2. This conclusion is further supported by the results of the short term study conducted by American Cyanamid which demonstrated a dosage related effect in both the incidence and size of the stones.
Also EPA toxicologists came to the same conclusion.
Source: (5)

Type of study: Evaluation
Year: 1985
Result: IARC evaluated the 2 NTP carcinogenesis assay (11). The other 2 carcinogenicity studies (25) and (6) were not included in the evaluation. The conclusion was that there is an "inadequate evidence" for carcinogenicity of melamine to experimental animals and no evaluation of the carcinogenicity of melamine to humans could be made.
Source: (9)

Type of study: Evaluation
Year: 1998
Result: IARC re-evaluated the results on melamine in 1998. Some citations from the summary of the draft report are:
"Human carcinogenicity data: No data were available to the Working Group.

Other relevant data: There is no evidence that melamine undergoes biotransformation. The urinary bladder tumours seen in male rats exposed to high doses of melamine appear to be produced by a non-DNA-reactive mechanism involving epithelial hyperplasia secondary to the presence of melamine-containing bladder stones. Consequently, bladder tumours would not be expected in either rodents or humans except at doses that produce bladder calculi. No data were available on the genetic and related effects of melamine in humans. It was not genotoxic in experimental systems.
Evaluation: There is *inadequate evidence* in humans for the carcinogenicity of melamine. There is *sufficient evidence* in experimental animals for the carcinogenicity of melamine under conditions in which it produces bladder calculi.
Overall evaluation: In making its overall evaluation, the Working Group noted that the non-DNA-reactive mechanism by which melamine produced urinary bladder tumours in male rats occurred only under conditions in which calculi were produced. Melamine is *not classifiable as to its carcinogenicity to humans (Group 3)*."

Source: (133)

Type of study: Evaluation
Year: 1985
Result: The induction of urolithiasis and its relation to bladder neoplasms was investigated for 3 substances, one of which is melamine. It was concluded that the bladder tumours were secondary to the development of calculi. Melamine is apparently nongenotoxic. Increased cell replication in the urothelium of the bladder caused by chronic physical injury was probably a major factor in the mechanism of induction of bladder tumours by bladder stones.
Source: (7)

Type of study: Evaluation; comparison with genotoxicity data.
Year: 1987 - 1991
Result: The carcinogenicity potency TD50, defined as "chronic dose rate which would halve the adjusted percentage of tumor-free animals at the end of a standard experiment time" was estimated to be 735 mg/kg bw/d for melamine. Melamine was classified as a non-genotoxic carcinogen.
Source: (104), (58), (129)

Type of study: Evaluation
Year: 1991, 1995
Result: The authors investigated the mechanism of non-genotoxic carcinogens. They proposed that the formation of bladder stones is necessary for tumor induction by certain non-genotoxic compounds, including melamine, following long-term administration at super-threshold doses. The differences between rodent and human bladders and their implications on the tumour formation are worked out.
Source: (38), (3)

5.8 Toxicity to Reproduction

Results: No indication of an effect to the reproductive organs was obtained from the repeated dose and chronic toxicity studies: mammary glands, ovaries, prostate,

seminal vesicles, testes and uterus were examined macroscopically and microscopically in 13-weeks and in chronic toxicity studies with rats and mice.
Source: (11)

5.9 Developmental Toxicity/Teratogenicity

Species: rat
Sex: female
Strain: Wistar
Route of admin.: with diet
Exposure period: day 6 through day 16 post coitum
Frequency of treatment: continously
Duration of test: until day 20 post coitum
Doses: 1500; 4500; 15000 mg/kg diet (ca. 136; 400; 1060 mg/kg body weight)
Control Group: concurrent, dosed with the feed alone
Method: OECD 414
Year: 1996
GLP: yes
Test substance: melamine ca. 100 %.
Result: Only maternal toxicity (decreased body weight and feed consumption, haematuria, indrawn flanks) was observed in the high dosed group during dosing period. At sacrifice reduced body weight was the only toxic sign.
No substance related findings were detected for gestational parameters, developmental toxicity including teratogenicity.
NOAEL for the dams = 4500 mg/kg diet (ca. 400 mg/kg body weight). NOAEL for the foetuses = 15000 mg/kg diet (ca. 1060 mg/kg body weight).
Source: (8)

Species: rat
Sex: female
Strain: Wistar
Route of admin.: i.p.
Exposure period: 4th and 5th or 7th and 8th or 11th and 12th day of gestation
Frequency of treatment: as mentioned above
Duration of test: 22 days
Doses: 70 mg/kg
Control Group:
Method:
Year: 1957
GLP:
Test substance:
Result: There were neither significant signs of maternal toxicity nor teratological effects. The study was not conducted according to current standards.
Source: (130)

5.10 Other Relevant Information

A. Specific Toxicities

Type: Biochemical or cellular interactions

Remark: Principal component of urinary bladder stones found in rats - after melamine feeding - is melamine.
Source: (19)

Type: Biochemical and cellular interactions
Remark: Spermidine/spermine N-acetyltransferase (a marker of cell proliferation) and ornithine decarboxylase (a marker of tumour promotion) were determined in papillomatosis and in normal epithelial tissue of the urinary bladder following feeding of male rats with 3 % melamine for 8 weeks.
Both enzyme activities were significantly higher in papillomas than in normal tissue.
Source: (88)

Type: Effects on tumor growth
Remark: The effect of melamine on the growth of transplanted "Walker carcinoma 256" was studied in rats. Tumor growth as measured by mass was increased by melamine compared to the control. Number of anaphases of the tumor tissue was slightly increased over controls.
Source: (65)

Type: V79 metabolic cooperation assay
Remark: Inhibition of metabolic cooperation between 6-thioguanine-sensitive and -resistant V79 Chinese hamster lung cells has been advocated as a method for detecting tumor promotors and teratogens. Melamine was inactive according to the criteria used.
Source: (134)

Type: Cytotoxicity
Remark: Cytotoxic action of melamine on certain tumor cell lines in vitro.
Source: (118), (117)

Type: other
Remark: Antitumorigenic properties of Hexamethylmelamine and its demethylated derivatives depended upon the methylgroups. Melamine which is totally demethylated was inactive.
Source: (78), (113)

B. Toxicodynamics, Toxicokinetics

Type: Metabolism
Remark: Male F-344 rats received a single oral dose of 0.38 mg 14C-melamine. Of 93 % of the dose excreted in the urine 90 % were excreted in the first 24 hours. Melamine was not metabolized, there was no binding or storage in organs. High levels of radioactivity were found only in the kidneys and the urine bladder. The elimination half-life in plasma was about 3 h. No residual radioactivity was observed at 24 h or later.
Source: (85)

Type: Metabolism
Remark: Studies on the metabolism of hexamethymelamine in humans and rats indicate that the s-triazine ring is resistant to metabolic cleavage in vivo.

Source: (135)

Type: Absorption
Remark: Intestinal distribution and absorption of melamine and its disposition in blood and urine were studied in male Wistar rats. In a 1-week feeding study, melamine was not absorbed in the stomach but monoexponentially in the small intestine. Melamine was also detected in the caecum and the large intestine, indicating the possibility that melamine affects intestinal microbial degradation. The half life of melamine in the ligated upper part of the small intestine was 37.9 min; the doubling time of melamine was 18.6 min in the blood and 2.9 min in the urine. Melamine injected into femoral vein was excreted monexponentially into the urine from blood.
Source: (125)

Type: Toxicodynamics
Remark: Investigation about the diuretic effects of melamine. Doses up to 20 mM/kg produced crystalluria in rats.
Source: (79)

Type: Toxicokinetics
Remark: Melamine acts as a diuretic in dogs and rats. Rats excreted 50 % of the substance within 6 h, dogs 60 to 86.5% within 24 h. Crystals found in urine were composed of dimelamine monophosphate. Also some experiments on pharmacological actions of melamine were performed. The authors describe forming of crystal compounds after the administration of high doses. One dog fed melamine, adeninesulfate and formoguanamine over a period of 6 months developped a bladder stone.
Source: (80)

5.11 Experience with Human Exposure

Remark: The abstract mentions chronic occupational diseases caused by melamine. No further data were presented.
Source: (92)

Remark: Workers engaged in the production of melamine-formaldehyde products had dermatoses. The authors consider changes to be due to irritation. The source also mentions that there seems to be no sensitivity to melamine.
Source: (123)

Remark: Case report of a worker who handled a melamine-formaldehyde resin. Patch tests with cobalt and formaldehyde gave a positive reaction. Additionally the man suffered from recurrent psoriasis for more than 40 years. No data about sensitizing properties of melamine are presented.
Source: (55)

Remark: Workers involved in the manufacture of melamine and dicyanid-diamide showed symptoms of allergic dermatitis. No further data concerning melamine were presented.
Source: (127)

Remark: Patch-Test signs of irritation/sensibilization in the persons examined (no further data).
Source: (45)

Remark: Shift workers are not exposed to melamine during routine production. Workers engaged in cleaning or filling or emergency operations may be exposed over some hours per week.
No effects to the production personal were found until today.
Source: Agrolinz Melamin GmbH, Austria.

Remark: A dust loading in the working area of 1.14 mg/m^3 was determined in a processing plant at 36 °C and a wind speed of 4.2 m/s.
Source: Agrolinz Melamin GmbH, Austria.

Remark: Workplace monitoring by personal air sampler, total inhalable dust.
5 measurements at a production site, 3 measurements at processing. All results were in the range of 0.1 to 1 mg/m^3.
Source: BASF AG, Germany, 1997.

Type of measurement: Migration of melamine into food.
Year: 1987.
Results: Acidic food (pH 2-5) is able to release traces of melamin from compression moulds made of melamine-formaldehyde resin after prolonged exposure (30 min) at high temperature (95 °C). 0.54 to 2.21 mg melamine / kg food were found in lemon and orange juice, in coffee and curdled milk under the described conditions.
Source: (10)

Type of measurement: Migration of melamine into food.
Year: 1986.
Method: Tableware cups made of melamine-formaldehyde resin were extracted with water, 4 % acetic acid, 20 % ethanol and n-heptane as food simulating solvents.
Results: 4 % acetic acid at high temperatures (95 °C) is able to release some melamine. The highest migration found was 42.9 ppm in 220 ml 4 % acetic acid when the migration test was repeated 7 times at 95 °C for 30 min. Melamine migrates only to a limited extent when used under moderate conditions such as noted in the Japanese Food Sanitation Law of 1982 but may migrate when used under more severe conditions.
Source: (72)

6. REFERENCES

(21) Acute Toxicity Data, J. American College Toxicol. 1, 110, 1990; cited in RTECS (115).

(22) Adema, D.M.M., The acute and chronic toxicity of melamine to Daphnia magna, TNO-report, prepared on behalf of DSM Central Laboratory, 1-10, Report no. CL 78/60, 1978.

(23) Adema, D.M.M., The influence of melamine on the egg-larval development of the fish species Jordanella floridae, TNO-Report No. CL82/108, 1982.

(24) American Cyanamid Company study; cited in (48), 1984.

(25) American Cyanamid Company, Melamine: acute and chronic toxicity, Report 55-21, unpublished data, 1955; cited also in (11), (97), (105), (47) as Shaffer C.B., ...

(26) American Cyanamid Company, unpublished data, Raltech Study No. 81560, 1981; cited in (87).

(27) American Cyanamid Company, unpublished data, Study No. PH 311-AC-002-82, 1982.

(28) American Cyanamid Company, unpublished data, Study No. PH 319-AC-002-82, 20.05.1982.

(29) BASF AG, Department of Toxicology; unpublished data (XIX/5), 23.04.1969.

(30) BASF AG, Octanol-Wasser-Verteilungskoeffizient Pow und Wasserlöslichkeit von Melamin, unpublished report BRU 88.067, 1988.

(31) BASF AG, Oekologielabor; unpublished report Öko-Nr. 1910405, 1991.

(32) BASF AG, Prüfung der biologischen Abbaubarkeit bzw. Eliminierbarkeit von Melamin im Standversuch nach Zahn-Wellens, Laboratory of Ecology and Environmental Analytics, unpublished report, Project No. 93/2364/10/2, 1993.

(33) BASF AG, Safety Data Sheet Melamine, 4/92.

(34) BASF AG, Sauerstoffverbrauchstest, Labor für Oekologie; unpublished report Nr. 01/88/0295, 1990.

(35) Biodegradation and Bioaccumulation Data of Existing Chemicals Based on the CSCL Japan, ed. by Chemicals Inspection and Testing Institute Japan, published by Japan Chemical Industry Ecology-Toxicology and Information Center, October 1992.

(36) BUA Report 105, Melamine, GDCh-Advisory Committee on Existing Chemicals of Environmental Relevance, 1992.

(37) Chapmann R.P., Averell P.R., Harries R.R., Ind. Eng. Chem. 35, 137, 1943; cited in (4).

(38) Cohen S.M. and Ellwein L.B., Genetic errors, cell proliferation, and carcinogenesis, Cancer Research 51, 6493-6505, 1991.

(39) Cohen S.M. and Lawson T.A., Rodent bladder tumors do not always predict for humans, Cancer Lett. 93, 9-16, 1995.

(40) Cook, A.M., Huetter, R., s-Triazine as nitrogen sources for bacteria, J. Agric. Food Chem. 29, 1135-1143, 1981.

(41) Crews G.M., Ripperger W., Kersebohm D.B. and Seeholzer J., Melamine and Guanamines, in Ullmann's Encyclopedia of Industrial Chemistry, Vol A16, p. 171-185, 5th ed., VCH Verlagsgesellschaft, 1990.

(42) DSM 1989, confidential information (brief 30-6-89 nr.2104); cited as source C8 in the

DSM Inventory of Data on Chemicals (prepared by BKH 20.01.92).

(43) DSM Research, Van't Oost E., Stofexplosie-eigenschappen van melamine, confidential report NC 90 2594, 1990.

(44) DSM: unpublished data (03.02.1993).

(45) ECETOC, Melamine, Joint assessment of commodity chemicals No.1, European Chemical Industry Ecology & Toxicology Centre, 1983.

(46) Elmore E. and Fitzgerald M.P., Evaluation of the Bioluminescence assays as Screens for Genotoxic Chemicals, Mutation and the Environment, Part D, pp. 379-387, Wiley-Liss Inc., 1990.

(47) EPA Chemical Hazard Information Profile, Draft report by Daugherty M.L., Oak Ridge National Laboratory, 1982.

(48) EPA, Cypromazine, proposed tolerance, Federal Register 49, No 83, 18121-18125, 1984.

(49) European Chemicals Bureau, IUCLID file on Melamine, European Commission, Ispra, Italy, public version, edition I on CD-ROM, 1966.

(50) European Chemicals Bureau, Technical Guidance Documents in support of the Commission Directive 93/67/EEC on risk assessment for new notified substances etc., EU, 1996.

(51) Fassett D.W. und Roudabush R.L., Lab.of Ind. Med., Eastman Kodak Co., unpubl. observations, < 1963; cited in: (105).

(52) FDA Cancer Assessment Committee; cited in (48), 1984.

(53) FESYP, European federation of associations of particleboard manufacturer, Annual report 1997/98, 146 - 152.

(54) Fimberger E.A., Bestimmung von Neben- und Abbauprodukten des Melamins mittels Kapillarelektrophorese und Abbauverhalten des Melamins in Kläranlagen, Diplom-Thesis, University of Salzburg, 1997.

(55) Fregert S., Formaldehyde dermatitis from a gypsum-melamine resin mixture, Contact Dermatitis 7, 56, 1981.

(56) Galloway S.M. et al.., Chromosome aberrations and sister chromatid exchange in Chinese hamster ovary cells: evaluation of 108 chemicals, Environ. Molec. Mut. 10 (Suppl.10), 1-175, 1987.

(57) Gmelins Handbuch der Anorganischen Chemie, 14 Kohlenstoff, Teil D1, page 361, Verlag Chemie, 8th edition, 1971.

(58) Gold L.S. et al., Summary of carcinogenic potency and positivity for 492 rodent carcinogens in the carcinogenic potency database, Environ. Health Perspect. 79, 259-272, 1989.

(59) Hauck, R.D., Stephenson,H.F., Nitrification of triazine nitrogen, J. Agric. Food Chem.12, 147-151, 1964.

(60) Haworth S. et al., Salmonella mutagenicity test results for 250 chemicals, Environ.Mutagen. Suppl.1, 3-142, 1983.

(61) Hazelton Raltech Report for American Cyanamid Company, 2-Year chronic feeding study of melamine in Fisher 344 rats, unpublished data, 1983; also cited in (111).

(62) Heck H.A. und Tyl R.W., The induction of bladder stones by tereohthalic acid, dimethyl

terephthalate, and melamine and its relevance to risk assessment, Regulat. Tox. Pharmacol. 5, 294-313, 1985.

(63) Heil J. and Reifferscheid G., Detection of mammalian carcinogens with an immunological DNA synthesis-inhibition test, Carcinogenesis 13, 2389-2394, 1992.

(64) Hellwig J., Gembrandt Ch. Hildebrandt B., Melamine - Prenatal Toxicity in Wistar Rats after oral Administration (Diet), Project No. 32R0242/94007, 1996.

(65) Hendry J.A., Cytotoxic agents: I, methylolamides with tumour inhibitory activity, and related inactive compounds, Brit. J. Pharmacol. 6, 201-234, 1951.

(66) Heukelekian H., Rand M.C., Journal Water Pollution Control Association 27, 1040-1053, 1955.

(67) Hirt R.C. et al., Vapor pressure of 2,4,6-triamino-s-triazine (melamine), J. Polymer Sci. XLIII, 319-323, 1960.

(68) Hockenbury M.R., Grady Jr. C.P.L., Inhibition of nitrification-effects of selected organic compounds, JWPCF 49(1), 768-777, 1977.

(69) IARC Monographs on the evaluation of the carcinogenic risk of chemicals to humans, Vol. 39, 333-346, 1985.

(70) Ishiwata H. et al., J. Food Hyg. Soc. Japan, 32, 408-413, 1991.

(71) Ishiwata H. et al., Liquid chromatographic determination of melamine in beverages, J. Assoc. Off. Anal. Chem., 70, 457-460, 1987.

(72) Ishiwata H. et al., Migration of melamine and formaldehyde from tableware made of melamine resin, Food Add. Contamin., 3, 63 - 70, 1986.

(73) Jansen B., unpubl. data, (1978), cited in (45).

(74) Jansen B.P., Memo 1982, (nr. CRO mk 82 359 mr-1), (1988); cited in: DSM, Inventory of data on chemicals, Melamine, RO471001/286J/D1, Delft, 20.01.92.

(75) Jutzi K. et al., The degradation pathway of the s-triazine melamine, Biochem. J. 208, 679-684, 1982.

(76) Kirk-Othmer, Encyclopedia of Chemical Technology, Vol. 14, p. 14, 216, 560, 741 and Vol. 16, p. 790, 793, 817, 1981.

(77) Koch, A., Onderzoek naar het effect van melamine in grondpercolaat op de wortelontwikkeling van kiemplanten, memoRes MK 86 769 BO-MVR, 1986.

(78) Lake L.M. et al., Toxicity and antitumor activity of hexamethylmelamine and its N-demethylated metabolites in mice with transplantable tumors, Canc. Res. 35, 2858-2863, 1975.

(79) Lipschitz W.L. and Hadidian Z., Amides, amines and related compounds as diuretics, J. Pharmacol. Exp. 81, 84-94, 1944.

(80) Lipschitz W.L. und Stokey E., The mode of action of three new diuretics: melamine, adenine and formoguanamine, J.Pharmacol.Exp.Ther. 83, 235-249, 1945.

(81) Litton Bionetics Inc. for DSM, Mutagenicity evaluation of melamine, unpublished data, LBI Project No. 2838, 1977.

(82) Litton Bionetics, unpublished data, 1977.

(83) Lüers H. and Roehrborn G., The mutagenic activity of ethyleneimino derivatives with

different numbers of reactive groups, Genet.Today Proc.Int.Congr. 1, 64-65, 1963, abstract.

(84) Lusby A.F. et al., Variation in mutagenicity of s-triazine compounds on 4 Salmonella strains, Environ. Mut. 1, 287-290, 1979.

(85) Mast R.W. et al., Metabolism, disposition and excretionof 14C-melamine in male in male Fischer 344 rats, Fd. Chem. Toxic. 21/6, 807-810, 1983.

(86) Mast R.W. et al., Mouse micronucleus assay of melamine, Envirn. Mutag. 4, 340-341, 1982.

(87) Mast R.W. et al., Mutagenicity testing of melamine, Toxicologist 2, 172, (1982), abstract.

(88) Matsui-Yuasa I. et al., Spermidine/spermine N-acetyltransferase, a new biochemical marker for epithelial proliferation in rat bladder, Jpn. J. Cancer Res. 83, 1037-1040, 1992.

(89) McGregor D.B. et al., Responses of the L5178Y tk^+/tk^- mouse lymphoma cell forward mutation assay: III. 72 coded chemicals, Environ.Molec.Mut. 12, 85-154, 1988.

(90) Melnick R.L. et al., Urolithiasis and bladder carcinogenicity of melamine in rodents, Toxicol.Appl.Pharmacol. 72, 292-303, 1984.

(91) Mirsalis J. et al., Induction of unscheduled DNA synthesis in hepatocytes following in vitro and in vivo treatment, Environ.Mutagen. 5, 482, 1983, abstract.

(92) Nargizyan G.A. et al., Occupational disease in the principle chemical industries of the Armenian SSR, Zh. Eksp. Klin. Med. 18, 101-104, 1978, cited in : Biol. Abstr. 68, 3836, 1979.

(93) Neis, J., DSM Melamine, Memo 1657/91 on Wassergefährdungsklasse Melamine, 31 July 1991.

(94) Niemi, G.J. et al., Environmental Toxicology and Chemistry 6, 515-527, 1987.

(95) NTP annual plan for the fiscal year 1986, p.74, 1986.

(96) NTP Chemical Repository, 1991, http://ehis.niehs.nih.gov/ntp/chem_hs.

(97) NTP,Carcinogenesis bioassay of melamine in F344/N rats and B6C3F1 mice (feed study), Technical Report Series No. 245, U.S. Department of Health and Human Services, 1983.

(98) Office of Health Studies, Chemicals in the Environment, Report on Environmental Survey and Wildlife Monitoring of Chemicals in F.Y. 1986 and 1987, Department of Environmental Health, Japan, 1989.

(99) Office of Health Studies, Chemicals in the Environment, Report on Environmental Survey and Wildlife Monitoring of Chemicals in F.Y. 1988 and 1989, Department of Environmental Health, Japan, 1991.

(100) Office of Health Studies, Chemicals in the Environment, Report on Environmental Survey and Wildlife Monitoring of Chemicals in F.Y. 1995, Department of Environmental Health, Japan, 1997.

(101) Ogasawara H. et al., Urinary bladder carcinogenesis induced by melamine in F344 male rats: correlation between carcinogenicity and urolith formation, Carcinogenesis 16, 2773-2777, 1995.

(102) Okumura M. et al., Relationship between calculus formation and carcinogenesis in the urinary bladder of rats administered the non-genotoxic agents, thymine or melamine, Carcinogenesis 13, 1043-1045, 1992.

(103) Oldersma H., Hanstveit A.O., The effect of the product melamine on the growth of the

green alga Scenedesmus pannonicus, TNO-report no. 81/188, 1-12, 1982.

(104) Parodi S. et al., Are genotoxic carcinogens more potent than nongenotoxic carcinogens?, Environ. Health Perspect. 95, 199-204, 1991.

(105) Patty's Industrial Hygiene and Toxicology, Vol. 2a, 3rd ed., p. 2769-2818, 1981.

(106) Perrella F.W. und Boutwell R.K., Triethylenemelamine: an initiator of two stage carcinogenesis in mouse skin which lacks the potential of a complete carcinogen, Canc.Letters 21, 37-41, 1983.

(107) Pharmakon Research Int. Inc., Genetic toxicology - Micronucleus test, Report for American Cyanamid Company, Study No. PH 309A-AC-001-81, unpublished data, 1981; also cited in: Mast R.W., et al., Environ. Mut. 4, 340-341, 1982.

(108) Philips F.S. und Thiersch J.B., The nitrogen mustard-like actions of 2,4,6-tris(ethylenimino)-s-triazine and other bis(ethylenimines), Pharmacol.Exp.Ther. 100, 398-407, 1950.

(109) Rainbauer H., Zeugnis über die Explosionsfähigkeit von 2 Staubproben, Sicherheitstechnische Prüfstelle des Unfallverhütungsdienstes der Allgemeinen Unfallversicherungsanstalt, 1989.

(110) Ramusino M.C. and Vailati G., Modification in Salmo gairdneri due to 2,4,6 triamino 1,3,5 triazine (melamine), Acta Embryol. Morphol. Exper. n.s. 3(1), 41-48, 1982.

(111) Rao G.N. et al., Chronic toxicity of melamine in Fischer 344 rats, Toxicologist 2, 179, (1982), abstract.

(112) Rijcken W.R.P., Primary skin irritation/corrosion study with melamine in the rabbit, confidential Notox project 146205 for DSM Melamine, 1995.

(113) Rosenkranz H.S. and Klopmann G., The structural basis of the mutagenicity of chemicals in Salmonella typhimurium: the National Toxicogy Program data base, Mutat. Res. 228, 51-80, 1990.

(114) Rossman T.G. et al., Performance of 133 compounds in the lambda prophage induction endpoint of the Microscreen assay and a comparison with S. typhimurium mutagenicity and rodent carcinogenicity assays, Mutat. Res. 260, 349-367, 1991.

(115) RTECS database, 1998.

(116) RTI, Evaluation of urolithiasis induction by melamine in male weanling Fischer 344 rats, Project No. 31T-2407 for American Cyanamid Company, unpublished data, 1982.

(117) Rutty C.J. and Abel G., In vitro cytotoxicity of the methylmelamines, Chem. Biol. Interactions 29, 235-246, 1980.

(118) Rutty C.J. und Connors T.A., In vitro studies with hexamethylmelamine, Biochem.Pharmacol. 26, 2385-2391, 1977.

(119) Sadtler standard spectra, Philadelphia, Pa., Sadtler Research Lab.

(120) Sasaki, S., The Scientific Aspects of the Chemical Substances Control Law in Japan, in Aquatic Pollutants:Transformation and Biological Effects, Hutzinger,O. et al., Pergamon Press, Oxford, 283-298, 1978.

(121) Seiler J.P., A survey on the mutagenicity of various pesticides, Experienta 29, 622-623, 1973.

(122) Shelby M.D. et al., Evaluation of a three-exposure mouse bone marrow micronucleus

protocol: Results with 49 chemicals, Environ. Mol. Mutagen. 21, 160-179, 1993.

(123) Soubrier R. and Burlet P., Dermatoses provoque par la melamine, Arch. Mal. Prof. Trav. Sec. Soc. 33, 202-204, 1972.

(124) SRC, 1988.

(125) Sugita T. et al.., Intestinal absorption and urinary excretion of melamine in male Wistar rats, J. Food Hyg. Soc. Japan 32, 439-443, 1991.

(126) Swope H.G. and Kenna M., Effect of organic compounds on biochemical oxygen demand, Sewage Industr. Wastes Engin., 467-468, 1950.

(127) Szczeklik-Franek A. and Masalska H., Occupational dermatoses, Wiad. Lek. 30, 1599-1602, 1977; also cited in Chem. Abstr. 88, 348, 1978.

(128) Tennant R.W. et al., Comparison of multiple parameters of rodent carcinogenicity and in vitro gegentic toxicity, Environ.Mut. 8, 205-227, 1989.

(129) Tennant R.W. et al., Prediction of chemical carcinogenicity in rodents from in vitro genetic toxicity assays, Science 236, 933-941, 1987.

(130) Thiersch J.B., Effect of 2,4,6, triamino-s-triazine (TR), 2,4,6 tris(ethyleneimino)-s-triazine (TEM) and N,N',N"-triethylenephosporamide (TEPA) on rat litter in utero, Proc.Soc.Biol.Med. 94, 36-43, 1957.

(131) TRGS 900, Technische Regeln für gefährliche Stoffe, Grenzwerte in der Luft am Arbeitsplatz, Germany, 1993.

(132) Ubaidullajev R.U. et al., Gigiena i Sanitariya, 58, 14-16, 1993; also cited in RTECS (115).

(133) Wilbourn, J.D., IARC - WHO, personal communication, 30 November 1998.

(134) Willington S.E. et al., Methods and criteria for assessing the activity of chemicals in the V79 metabolic cooperation assay, Mutat. Res. 216, 283, 1989.

(135) Worzalla J.F. et al., Metabolism of Hexamethylmelamine-Ring-^{14}C in Rats and Man, Cancer Res. 34, 2669-2674, 1974.

EXTRACT FROM IRPTC LEGAL FILES

```
file: 17.01 LEGAL   rn : 303263
systematic name:1,3,5-Triazine-2,4,6-triamine
common name    :Melamine
reported name  :MELAMINE
cas no         :108-78-1            rtecs no       :OS0700000
area          : CAN                 type          : REG
 ---------------------------------
|subject|specification|descriptor|
|-------+-------------+----------|
| USE   |    OCC      |   RQR    |
| STORE |             |          |
| LABEL |             |          |
 ---------------------------------
Ingredient Disclosure List - Concentration: 1% weight/weight. The
Workplace Hazardous Materials Information System (WHMIS) is a national
system providing information on hazardous materials used in the
workplace. WHMIS is implemented by the Hazardous Products Act and the
Controlled Products Regulations (administered by the Department of
Consumer and Corporate Affairs). The regulations impose standards on
employers for the use, storage and handling of controlled products. The
regulations also address labelling and identification, employee
instruction and training, as well as the upkeep of a Materials Safety
Data Sheet (MSDS). The presence in a controlled product of an ingredient
in a concentration equal to or greater than specified in the Ingredient
Disclosure List must be disclosed in the Safety Data Sheet.
entry date: APR 1991                          effective date: 31DEC1987

amendment: CAGAAK, CANADA GAZETTE PART II, 122 , 2 , 551 , 1988


                                  *******


file: 17.01 LEGAL   rn : 1122591
systematic name:1,3,5-Triazine-2,4,6-triamine
common name    :Melamine
reported name  :MELAMINE
cas no         :108-78-1            rtecs no       :OS0700000
area          : RUS                 type          : REG
 ---------------------------------
|subject|specification|descriptor|
|-------+-------------+----------|
| AIR   |    OCC      |   MAC    |
|       |             |   CLASS  |
 ---------------------------------
CLV: 0.5MG/M3 (AEROSOL) HAZARD CLASS: II
entry date: MAY 1990                          effective date: 01JAN1989

amendment: GOSTS*, GOSUDARSTVENNYI STANDART SSSR(STATE STANDARD OF
           USSR), 12.1.005 , , , 1988


                                  *******


file: 17.01 LEGAL   rn : 1302367
systematic name:1,3,5-Triazine-2,4,6-triamine
common name    :Melamine
reported name  :MELAMINE
cas no         :108-78-1            rtecs no       :OS0700000
area          : USA                 type          : REG
```

```
 --------------------------------
|subject|specification|descriptor|
|-------+-------------+----------|
| FOOD  |    ADDIT    |   RSTR   |
| TRANS |             |   RSTR   |
| STORE |             |   RSTR   |
| PACK  |             |   RSTR   |
 --------------------------------
; Summary - THIS SUBSTANCE IS INCLUDED ON A LIST OF SUBSTANCES USED TO
PREPARE ADHESIVES WHICH MAY BE SAFELY USED AS COMPONENTS OF ARTICLES
INTENDED FOR USE IN PACKAGING, TRANSPORTATION, OR HOLDING FOOD IN
ACCORDANCE WITH THE FOLLOWING PRESCRIBED CONDITIONS: SUBSTA NCE MUST BE
SEPARATED FROM THE FOOD BY A FUNCTIONAL BARRIER, MUST NOT EXCEED LIMITS
OF GOOD MANUFACTURING PRACTICE USED WITH DRY FOODS, OR NOT EXCEED TRACE
AMOUNTS AT SEAMS AND EDGE EXPOSURES WHEN USED WITH FATTY AND AQUEOUS
FOODS. ALSO REGULATED BY SEA M INTEGRITY, LABELING STANDARDS, AND ANY
PROVISION UNDER 21 CFR 175
entry date: NOV 1991                          effective date:      1977

title: SUBSTANCES FOR USE ONLY AS COMPONENTS OF ADHESIVES
original : FEREAC, FEDERAL REGISTER, 42 , , 14534 , 1977
amendment: CFRUS*, CODE OF FEDERAL REGULATIONS, 21 , 175 , 105 , 1988


                                 *******


file: 17.01 LEGAL   rn : 1336171
systematic name:1,3,5-Triazine-2,4,6-triamine
common name    :Melamine
reported name  :MELAMINE
cas no         :108-78-1            rtecs no       :OS0700000
area          : USA                 type          : REG
 --------------------------------
|subject|specification|descriptor|
|-------+-------------+----------|
| AIR   |    EMI      |   RQR    |
| SOIL  |    EMI      |   RQR    |
| AQ    |    EMI      |   RQR    |
| MANUF |    EMI      |   RQR    |
 --------------------------------
; Summary - FACILITIES THAT EXCEEDED A MANUFACTURING, IMPORTATION, OR
PROCESSING THRESHOLD OF 25,000 LBS OR THE USE OF 10,000 LBS FOR THIS
CHEMICAL MUST REPORT TO EPA ANY RELEASES OF THE CHEMICAL (OR CATEGORY
CHEMICAL) TO AIR, LAND, WATER, POTW, UNDERGROUND INJECTIO N, OR OFF SITE
TRANSFER. THIS REGULATION COVERS STANDARD INDUSTRIAL CLASSIFICATION
(SIC) CODES 20-39 ONLY).
entry date: OCT 1991                          effective date:      1987

title: SUPERFUND AMENDMENTS AND REAUTHORIZATION ACT, TITLE III. EPCRA
SECTION 313 LIST OF TOXIC SUBSTANCES
original : CFRUS*, CODE OF FEDERAL REGULATIONS, 40 , 372 , 65 , 1988
amendment: CFRUS*, CODE OF FEDERAL REGULATIONS, 40 , 372 , 65 , 1988


                                 *******


file: 17.01 LEGAL   rn : 1408459
systematic name:1,3,5-Triazine-2,4,6-triamine
common name    :Melamine
reported name  :2,4,6-TRIAMINO-1,3,5-TRIAZINE
```

```
cas no         :108-78-1            rtecs no       :OS0700000
area          : EEC                 type          : REG
 --------------------------------
|subject|specification|descriptor|
|-------+-------------+----------|
| FOOD  |             |   RQR    |
| GOODS |             |   MXL    |
| GOODS |             |   PRMT   |
 --------------------------------
THE SUBSTANCE IS INCLUDED IN THE LIST OF AUTHORIZED MONOMERS AND OTHER
STARTING SUBSTANCES, WHICH SHALL BE USED FOR THE MANUFACTURE OF PLASTICS
AND ARTICLES INTENDED TO COME INTO CONTACT WITH FOODSTUFFS. THE USE OF
THE SUBSTANCE IS SUBJECT TO THE RESTRICTIONS SPECIFIED THEREIN. SPECIFIC
MIGRATION LIMIT: 30 MG/KG. VERIFICATION OF COMPLIANCE WITH THE MIGRATION
LIMITS SHALL BE CARRIED OUT IN ACCORDANCE WITH DIRECTIVES 82/711/EEC AND
85/572/EEC.  SFER. THIS REGULATION COVERS STANDARD INDUSTRIAL
CLASSIFICATION
(SIC) CODES 20-39 ONLY).
entry date: OCT 1991                          effective date:      1987
title: SUPERFUND AMENDMENTS AND REAUTHORIZATION ACT, TITLE III. EPCRA
SECTION 313 LIST OF TOXIC SUBSTANCES
original : CFRUS*, CODE OF FEDERAL REGULATIONS, 40 , 372 , 65 , 1988
entry date: SEP 1995                          effective date: 01JAN1991

title: COMMISSION DIRECTIVE OF 23 FEBRUARY 1990 RELATING TO PLASTICS
MATERIALS AND ARTICLES INTENDED TO COME INTO CONTACT WITH FOODSTUFFS
(90/128/EEC)
original : OJEC**, OFFICIAL JOURNAL OF THE EUROPEAN COMMUNITIES, L75 , ,
           19 , 1990
amendment: OJEC**, OFFICIAL JOURNAL OF THE EUROPEAN COMMUNITIES, L90 , ,
           26 , 1993


                                 *******


file: 17.01 LEGAL   rn : 1470373
         !!! WARNING - not original IRPTC record - WARNING !!!
systematic name:1,3,5-Triazine-2,4,6-triamine
common name    :Melamine
reported name  :MELAMINE
cas no         :108-78-1            rtecs no       :OS0700000
area          : EEC                 type          : REG
 --------------------------------
|subject|specification|descriptor|
|-------+-------------+----------|
| MANUF |    INDST    |   CLASS  |
| IMPRT |    INDST    |   CLASS  |
 --------------------------------
The substance is included in a list of existing substances produced or
imported within the Community in quantities exceeding 1000 tonnes per
year. - A system of data reporting by any manufacturer who has produced
or any importer who has imported the substance, as such or in a
preparation, in quanities exceeding 10 tonnes per year is established.
entry date: AUG 1999                          effective date: 04JUN1993

title: Council Regulation (EEC) No 793/93 of 23 March 1993 on the
evaluation and control of the risks of existing substances
original : OJECFC, Official Journal of the European Communities, L84 , ,
           1 , 1993
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