SUBSTANCE EVALUATION REPORT

Background document for the purpose of substance evaluation under REACH

for

Substance Name: 1,3,5-trioxane
EC Number: 203-812-5
CAS Number: 110-88-3

Evaluating Member State: Poland
Dated: 27 February 2014

Evaluating Member State Competent Authority

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Conclusions of the most recent evaluation step	Tick relevant box(es)
Concern not clarified; Need to request further information from the Registrant(s) with the draft decision	
Concern clarified; No need of further risk management measures	
Concern clarified; Need for risk management measures; RMO analysis to be performed	
Other: Need for harmonised classification and labelling as an eye irritant category 2 on the basis of available data	X

DISCLAIMER

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EXECUTIVE SUMMARY

Grounds for concern

1,3,5-trioxane (CAS No: 26471-62-5) has been proposed for substance evaluation based on Article 44 of the REACH Regulation.
1,3,5-trioxane was included into the CoRAP on account of the following reasons:
- as a suspected CMR (Repr 2),
- as a suspected sensitiser and
- as a suspected PBT substance.

The concerns were also related to the wide dispersive use and high aggregated tonnage.
The aim of evaluation process was to clarify the initial concerns that the manufacture of 1,3,5-trioxane could pose a risk to human health or the environment.

During the evaluation also other concern was identified. The additional concern was:

- Need for classification as an eye irritant category 2 according to Regulation (EC) No 1272/2008 (CLP) classification criteria, on the basis of available information

Procedure

The evaluation was performed on the basis of registration dossier (IUCLID file) and Chemical Safety Report (CSR) submitted by the lead registrant and the CSRs submitted by the other registrants as well as on other, additional information available in scientific databases and publications. In IUCLID there were 9 registration dossiers and 9 CSRs. All of them, particularly the documentation of the lead registrant, were analysed with attention.

All the available information was assessed regarding and reliability for evaluation of the main grounds of concern as well as other effects of 1,3,5-trioxane on human health and the environment. In addition, that information was compared among the registration dossiers.

The assessment of exposure was performed with the tool ECETOC Targeted Risk Assessment v. 2.0 Programme. The exposure was assessed taking into consideration the information included in the descriptions of each exposure scenario (Chapter 9 of CSR. Exposure Assessment). The data on environmental effects was verified by the evaluator using European Union System for the Evaluation of Substances (EUSES).
The results of the evaluation are documented in this report.

Physical and chemical properties

The physical and chemical properties of 1,3,5-trioxane were evaluated.

Effects on human health

The evaluation of toxicity of 1,3,5-trioxane included all human health endpoints. A particular interest was directed to:
- reprotoxic effect
- irritating effect on respiratory system (1,3,5-trioxane is classified regarding specific target organ toxicity - single: STOT Single Exp. 3 (Hazard statement: H335: May cause respiratory irritation.). Route of exposure: Inhalation)
- eye irritation
- sensitizing properties

Effects on environment

The environmental hazard assessment of 1,3,5-trioxane was evaluated. Potential PBT properties were particularly considered during this work.

Worker exposure

Information on uses and occupational exposure to 1,3,5-trioxane was evaluated. The exposure scenarios for workers were checked with regard to operational condition and information about risk management measures.
All calculations were derived from modeling using the program ECETOC TRA v.2 and have been checked by the evaluator.

Consumer exposure

Consumer exposure was not assessed as non consumer uses have been registered for 1,3,5-trioxane.

Conclusions

Physical and chemical properties

According to REACH requirements: Annex VI, section 2.3 (and in Data Submission Manual Part 18 – "How to report the substance identity in IUCLID 5 for registration under REACH"), the concentration of the main constituents shall be provided as a range with upper and lower limits (Annex VI, section 2.3.1).
The concentration range shall also be provided for the impurities (Annex VI, section 2.3.3,).

The physical and chemical information was analyzed in terms of classification of 1,3,5-trioxane. On the basis of physico-chemical data the substance is classified as highly flammable (CLP Harmonised Classification: Flam. Solid 1, H228), according to the results of key and supporting studies submitted by the registrant. The classification is considered appropriate.

Human health

Evaluation of existing information confirmed that 1,3,5-trioxane has a low toxicity after an oral, inhalation and dermal exposure. The acute oral LD50 in rats is greater than 2000 mg/kg bw (3200 mg/kg bw indicated in key study), acute inhalation LC50 in rats greater than 39.2 mg/L and acute dermal LD50 in rabbits is greater than 2000 mg/kg bw (>3980 mg/kg bw indicated in key study). The classification of 1,3,5-trioxane regarding acute toxicity is not required.

1,3,5-trioxane has been evaluated for acute toxicity by all three of the usual routes of exposure and the results demonstrated that the substance has low potential for producing acute toxicity.

The results of skin irritation revealed no irritant potential of 1,3,5-trioxane in both key and supporting studies submitted by the registrant. The additional study indicated no irritating properties of the substance. Therefore classification of 1,3,5-trioxane regarding skin irritation is not required.

Evaluation of 1,3,5-trioxane effects on the eyes of rabbits was based on the nature, intensity and reversibility of the responses. According to key study, 1,3,5-trioxane resulted in moderate irritation of the conjunctiva and mild chemosis. Both changes were reversible within 72 hours. These symptoms do not provide a basis for classification.
Supporting study revealed mild to moderate irritation of conjunctiva, mild chemosis and corneal opacity with mean value = 1 for two rabbits. The changes were fully reversible within 8 days. According to CLP Regulation, 1,3,5-trixane fulfils classification criteria as irritating to eyes category 2.
There are available three other studies. The first one showed mild corneal opacity, mild chemosis and moderate conjunctival irritation which were reversible within 10 days. On the base of these results classification of 1,3,5-trioxane is not needed.
According to the two other studies trioxane is severely irritating for the eyes although the observed changes are reversible within 6 or 10 days after treatment in the first and second study respectively.

The results of available studies demonstrate eye irritating properties of 1,3,5-trioxane. Therefore the appropriate is to classify the substance as an eye irritant category 2, according to CLP classification criteria.

Repeated inhalation exposure to 1,3,5-trioxane resulted in reversible signs of respiratory tract irritation expressed as increased secretory response and desquamation of mucosa of the nasal cavity. Simultaneously, the other study

shows increased lymphocytic infiltrations in the larynx and trachea, proliferation of the peribronchial lymphatic tissue, and planoepithelial metaplasia of the bronchial epithelium. Thus, the assessment confirmed the harmonised classification of the substance as STOT Single Exp.3 (Hazard statement H335, May cause respiratory irritation).

The key study submitted by the registrant as well as other available scientific publications did not show 1,3,5-trioxane as a skin sensitizer, although it is known that during 1,3,5-trioxane degradation small amounts of skin sensitiser - formaldehyde can be released. Therefore the relevant information should be communicated in Safety Data Sheet to protect susceptible individuals.

The repeated dose toxicity study was conducted following oral and inhalation exposure. It was scientifically unjustified to conduct studies on dermal toxicity as studies of two other routes of exposure were available. Moreover, 1,3,5-trioxane is not irritating or sensitizing to the skin.
In a 90 days gavage study no signs of toxicity were observed in the highest tested dose level (NOAEL 300 mg/kg bw/d). In a 12 days inhalation study signs of respiratory irritation were observed in all exposed groups without signs of systemic toxicity. A NOAEC of 3.62 mg/l was derived based on decreased spleen weights. 1,3,5-trioxane is a respiratory irritant. The nose is a target organ.

The available in vitro data on genotoxicity were almost all negative. The tests employing bacteria and cells of Chinese hamster produced only negative effects. The test in mouse lymphoma cells gave a positive result when carried out in the presence of a metabolic activation system. However, the outcome of the parallel test without metabolic activation was negative. Both tests were performed using very high trioxane concentration, which resulted in cytotoxicity in the first test (with metabolic activation). This mutagenic effect was directly linked to the cytotoxicity so the relevance of that result must be questionable.
1,3,5-trioxane did not induce micronuclei formation or DNA damage in a micronucleus test, dominant lethal assay and unscheduled DNA synthesis.

No results are available from carcinogenicity studies in vivo. The data obtained from in vitro study showed no evidence of transformation the cell colonies thus the substance did not demonstrate carcinogenic potential.

Available studies on reproductive toxicity indicates that 1,3,5-trioxane does not exhibit a potential for toxicity to fertility but results in foetal lethality, retarded foetal growth and congenital malformations at the dose levels with less maternal toxicity. Studies confirm the applicable classification of 1,3,5-trioxane as reprotoxic category 2 (CLP Harmonised Classification: H361: May damage the unborn child).

The substance is appropriately classified as irritating to respiratory system and toxic for reproduction.
Based on the results of available studies it is concluded that 1,3,5-trioxane fulfils classification criteria as an eye irritant. Therefore the evaluator recommends to classify 1,3,5-trioxane as an eye irritant category 2 according to CLP, based on the results of studies already performed.

Environment

The information about environmental fate properties and ecotoxicity was evaluated on the basis of submitted information. In some cases the registrants do not provide experimental study results but apply adaptation rules to standard information requirements.

Fate and behaviour in the environment

1,3,5-trioxane is slowly hydrolysed and slowly degraded by photochemical process. It is easily eliminated from water and inherently biodegradable. It shows low adsorptive property, the value of log K_{oc} of 1,3,5-trioxane is equal -0.416. Based on that, 1,3,5-trioxane is considered to be mobile in sediments and soils. The low adsorptive property indicates as well that soil and sediment are not expected to be the main target compartments for exposure assessment. The distribution modelling confirms distributing of the substance only in air (19.95%) and water (80,05%). Besides, according to the registrant's CSR direct exposure of soil to 1,3,5-trioxane is unlikely. The Henry's Law constant (0.57 Pa m^3/mol) and the vapour pressure (11 hPa at 20 °C) of 1,3,5-trioxane indicate that the substance is volatile.
The bioaccumulation is not expected for 1,3,5-trioxane because the calculated log Kow of this substance is equal - 0.5.
No bioaccumulation properties of 1,3,5-trioxane in aquatic and terrestrial organisms indicates that the secondary poisoning study is not needed.

Evaluation of P B T/vPvB Properties

1,3,5-trioxane is persistent in the environment, has low bioaccumulation potential and it is toxic therefore 1,3,5-trioxane meets the criteria as a substance persistent in the environment (P) and toxic (T) but does not meet the criteria for bioaccumulation (B).
According to the guidance on PBT assessment (R.11, 2012), substances are considered as PBT (or vPvB) when they fulfil the criteria for all three (or two) inherent properties P, B an T (or vP and vB). As 1,3,5-trioxane does not fulfil B criterion it is not PBT substance.

Ecotoxicology

Ecotoxicological data indicates that 1,3,5-trioxane has not acute or chronic effects to fish and aquatic invertebrates ant it is not acute harmful to algae and cyanobacteria.
The physicochemical information demonstrates that 1,3,5-trioxane is not adsorptive (Log Koc = -0.416) or bioaccumulative (Log Pow = -0.5) so a significant distribution into the sediment compartment and a considerable exposure of sediment organisms is not expected.

The data on environmental toxicity for 1,3,5-trioxane includes as follows:
LC50 (96 h) 4000 mg/L for freshwater fish
LC50 (96 h) 16350 mg/L for saltwater fish
EC50 (48 h) >1000 mg/L for freshwater invertebrates
EC50 (72 h) 500 mg/L for freshwater algae

The evaluation of available toxicity data for fish, aquatic invertebrates and aquatic plants indicates that the potential hazard of 1,3,5-trioxane to aquatic organism is low and does not warrant classification.

A relevant exposure of soil macroorganisms and microorganisms and terrestrial arthropods and plants is not expected.
1,3,5-trioxane does not deplete the ozone layer.
The inhibition of the degradation activated sludge due to 1,3,5-trioxane is not anticipated. The PNEC for sewage treatment plant is calculated correctly.

Worker exposure

Due to relatively high vapour pressure of 1,3,5-trioxane, there is a high concern for potential risk to workers.
The exposure of workers has been calculated using ECETOC TRA v.2 tool. Exposure to the liquid form has been used due to the high vapour pressure and in order to take into account formation of vapour. All calculations provided by the registrant were checked by the evaluator and concluded as correct.
The substance is classified as irritating to the respiratory tract, therefore the Risk Management Measures of wearing respiratory protection and using Local Exhaust Ventilation is implemented in contributing scenarios with potential inhalation exposure. In all cases Risk Characterisation Ratios (RCRs) ratio was < 1. The RCRs show that potential risks for worker health are adequately controlled under the conditions of inhalation and dermal exposure. Therefore it is concluded that the use of 1,3,5-trioxane in industrial and professional settings is safe for workers under the specified condition of exposure.

Conclusions related to the concern

1. Basic grounds of concern

The grounds of concern listed in Justification document for the selection of the candidate CoRAP substance do not need additional clarification. On the basis of available information, 1,3,5-trioxane is not sensitizer or PBT substance. Classification regarding reprotoxicity is appropriate.

2. Established concern

Assessment of irritating effects led to a recommendation for classification as an eye irritant category 2. Of the five available results three indicates irritating properties of the substance and according to other two there is no need for classification although some changes were observed. It is important to mention that these data are sufficient for the classification purpose and no additional studies are required.

Statement of reasons

Physical and chemical properties

On the basis of physico-chemical data the substance is classified as highly flammable. The classification is considered appropriate.

Human health

The existing information is sufficient to conclude that exposure to 1,3,5-trioxane has been linked with the respiratory tract irritation and reproductive toxicity. The classification as reprotoxic and respiratory irritant is considered relevant.
On the base of available data the classification as an eye irritant is proposed by the evaluator.

P, B and T Properties

1,3,5-trioxane meets P and T but not B criterion, therefore it does not belong to PBT group.
The evaluation of available toxicity data for fish, aquatic invertebrates and aquatic plants indicates that the potential hazard of 1,3,5-trioxane to aquatic organism is low and does not warrant classification due to environmental hazard.

Environmental hazard assessment

1,3,5-trioxane is not distributed to soil and to sediment and both compartments are not expected to be the main targets for exposure assessment.

Occupational exposure
Nine uses by workers in industrial settings and four by professional workers were identified by the registrants. Detailed occupational conditions are presented in CSRs (Chapters: Exposure Assessment and Risk Characterisation). The exposure estimation calculated using ECETOC TRA tool indicates that there is no risk for workers exposed occupationally to 1,3,5-trioxane as well as for professional workers. In all cases the RCR ratio for inhalation and dermal exposure was less than 1. Therefore it is concluded that the risk is properly controlled.

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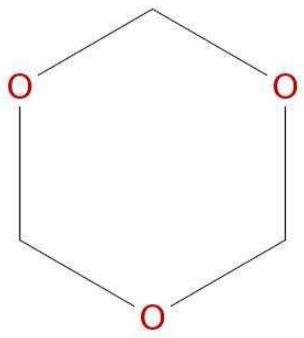
1. IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

1.1. Name and other identifiers of the substance

The substance **1,3,5-trioxane** is a mono constituent substance (origin: organic) having the following characteristics and physical–chemical properties.
The following public name is used: **1,3,5-trioxane.**

Table 1. Substance identity

EC number:	203-812-5
EC name:	1,3,5-trioxane
CAS number (EC inventory):	110-88-3
CAS name:	1,3,5-trioxane
IUPAC name:	1,3,5-trioxane
Other names:	1,3,5-Trioxacyclohexane; s-Trioxane; Trioxymethylene, Trioxin
Annex I index number:	605-002-00-0
Molecular formula:	C3H6O3
Molecular weight range:	90.0779



1.2. Composition of the substance - Confidential

Evaluator's comment regarding the concentration range of the main constituent and impurities:

According to REACH requirements: Annex VI, section 2.3 (and in Data Submission Manual Part 18 – "How to report the substance identity in IUCLID 5 for registration under REACH") the concentration of the main constituents shall be provided as a range with upper and lower limits (Annex VI, section 2.3.1).
The concentration range shall also be provided for the impurities (Annex VI, section 2.3.3,).
As the lack of this information is inconsistent with the provisions of the REACH, the evaluating MSCA recommends that registration dossiers should be updated.

1.3. Physicochemical properties

Table 2. Physicochemical properties

Property	Results	Value used for CSA / Discussion
Physical state at 20°C and 1013 hPa	solid Form: solidified melt Colour: white Odour: ethanol-like	The substance is a solid with a rather high vapour pressure. **Value used for the worker exposure estimates, calculated with the ECETOC TRA tool:** liquid
Melting / freezing point	62 °C	**Value used for CSA:** 62 °C at 1013 hPa
Boiling point	115 °C at 1013.25 hPa	**Value used for CSA:** 115 °C at 1013 hPa
Relative density	1.39 g/cm3 at 20 °C	**Value used for CSA:** 1.39 g/cm3 at 20 °C
Vapour pressure	11 hPa at 20 °C 800 hPa at 115 °C	**Values used for CSA:** 11 hPa at 20 °C 800 hPa at 115 °C
Surface tension	not surface active	Based on chemical structure, no surface activity is predicted.
Water solubility	172 g/l at 20 °C	**Value used for CSA:** 172 g/L at 20 °C
Partition coefficient n-octanol/water (log value)	-0.5 at 25 °C	**Value used for CSA:** Log Kow (Pow): -0.5 at 25 °C
Flash point	Not applicable	The substance is a solid.
Flammability	Highly flammable.	**Value used for CSA:** flammable
	The substance has no pyrophoric properties and does not liberate flammable gases on contact with water.	Flammability is derived from burning time test (UN) Based on chemical structure pyrophoric properties and flammability in contact with water are not to be expected.
Explosive properties	non explosive	**Value used for CSA:** non explosive There are no chemical groups associated with explosive properties present in the molecule.
Self-ignition temperature	not applicable	The substance is a solid with a melting point < 160°C.
Oxidising properties	no oxidising properties	**Value used for CSA:** Oxidising: no The Substance is highly flammable and incapable of reacting exothermically with combustible materials.
Granulometry	not applicable	Substance is marketed or used in a non solid or granular form (hot melt). No dust is formed during the handling of flakes, because - inter alia - the material is hygroscopic.
Stability in organic solvents and identity of relevant degradation products	not applicable	The stability of the substance is not considered as critical.
Dissociation constant	not applicable	The substance does not contain any ionic structure.
Viscosity	not relevant	The substance is a solid at 20 °C

Data waiving

The data on surface tension, flash point, explosive properties, self-ignition temperature, oxidizing properties, granulometry, stability in organic solvents and identity of relevant degradation products, dissociation constant and viscosity is waived. The registrant referred to the relevant annexes of REACH Regulation.

2. MANUFACTURE AND USES

Quantities 100,000 - 1,000,000 tonnes per annum (ECHA data base on registered substances).

2.1. Manufacture

According to CSRs submitted by the registrants, 1,3,5-trioxane is manufactured in the EU or outside EU and imported into EU.
It is used for production of polyacetals.

2.2. Identified uses

Uses by workers in industrial settings

Manufacture of 1,3,5-trioxane

Environmental release category (ERC):
ERC 1: Manufacture of substances
Process category (PROC):
PROC 1: Use in closed process, no likelihood of exposure
PROC 8a: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities
PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities

Polymerization of 1,3,5-trioxane

Environmental release category (ERC):
ERC 6c: Industrial use of monomers for manufacture of thermoplastics
Process category (PROC):
PROC 1: Use in closed process, no likelihood of exposure
PROC 8a: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities
PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities

Use as monomer for polymers and thermoplastics

Environmental release category (ERC):
ERC 6c: Industrial use of monomers for manufacture of thermoplastics
Process category (PROC):
PROC 2: Used in close, continuous process with occasional controlled exposure

Synthetise polymer acetal copolymer

Environmental release category (ERC):
ERC 1: Manufacture of substances
Process category (PROC):
PROC 4: Use in batch and other process (synthesis) where opportunity arises
PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated fiacilities
PROC 9: Transfer of substance or preparation into small containers (dedicated filling line, including weighing)

Monomer in an imported polymer

Environmental release category (ERC):
ERC 0: Other: The substance is a part of polymer, won’t be released to the environment
Process category (PROC):
PROC 0: Other: Manipulation of the polymer

Industrial manufacture of coatings and paints with the substance as a binding agent
Environmental release category (ERC):
ERC 2: Formulation of preparations
Process category (PROC):
PROC 5: Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact)
PROC 8a: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities
PROC 9: Transfer of substance or preparation into small containers (dedicated filling line, including weighing)

Industrial use of coatings and paints containing the substance

Environmental release category (ERC):
ERC 5: Industrial use resulting in inclusion into or onto a matrix
Process category (PROC):
PROC 7: Industrial spraying
PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities
PROC 10: Roller application or brushing
PROC 13: Treatment of articles by dipping and pouring

Use of the substance as laboratory chemical

Environmental release category (ERC):
ERC 8c: Wide dispersive indoor use resulting in inclusion into or onto a matrix

Process category (PROC):
PROC 15: Use as laboratory reagent

Uses by professional workers

Monomer in an imported polymer

Environmental release category (ERC):
ERC 0: Other: The substance is a part of polymer, won't be released to the environment
Process category (PROC):
PROC 0: Other: Manipulation of the polymer

Professional indoor use of coatings and paints containing the substance

Environmental release category (ERC):
ERC 8c: Wide dispersive indoor use resulting in inclusion into or onto a matrix
Process category (PROC):
PROC 8a: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities
PROC 10: Roller application or brushing
PROC 11: Non industrial spraying
PROC 13: Treatment of articles by dipping and pouring

Professional outdoor use of coatings and paints containing the substance

Environmental release category (ERC):
ERC 8f: Wide dispersive outdoor use resulting in inclusion into or onto a matrix

Process category (PROC):
PROC 8a: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities
PROC 10: Roller application or brushing
PROC 11: Non industrial spraying
PROC 13: Treatment of articles by dipping and pouring

Use of the substance as laboratory chemical

Environmental release category (ERC):
ERC 8c: Wide dispersive indoor use resulting in inclusion into or onto a matrix

Process category (PROC):
PROC 15: Use as laboratory reagent

Uses advised against
All uses apart from that intended by the manufacturer are advised against.

Summary

1,3,5-trioxane is used by workers in industrial settings in the following processes:
- manufacturing and polymerization of 1,3,5-trioxane,
- as monomer for polymers and thermoplastics and in an imported polymer,
- in synthesis polymer acetal copolymer,
- industrial manufacture of coatings and paints with the substance as a binding agent,
- industrial use of coatings and paints containing the substance,
- as laboratory chemical

and

by professional workers in:
- professional indoor and outdoor use of coatings and paints containing the substance,
- as laboratory chemical,
- as monomer of an imported polymer.

3. CLASSIFICATION AND LABELLING

3.1. Classification and labelling according to CLP / GHS

Implementation: EU

Classification

For physicochemical properties 1,3,5-trioxane is classified as follows:
- Flammable solids: Flam. Solid 1 (Hazard statement: H228: Flammable solid.)

For health hazards 1,3,5-trioxane is classified as follows:
- Reproductive Toxicity: Repr. 2 (Hazard statement: H361d: May damage the unborn child)
- Specific target organ toxicity - single: STOT Single Exp. 3 (Hazard statement: H335: May cause respiratory irritation.). Route of exposure: Inhalation

1,3,5-trioxane is not classified for environmental hazards

Labelling

Signal word: Warning

Hazard pictogram:

GHS02: flame

GHS07: exclamation mark

GHS08: health hazard

Hazard statements:

H228: Flammable solid.
H361d: May damage the unborn child.
H335: May cause respiratory irritation.

Precautionary statements:

P273: Avoid release to the environment.
P280: Wear protective gloves/protective clothing/eye protection/face protection.
P284: Wear respiratory protection.
P308+P313: IF exposed or concerned: Get medical advice/attention.
P403+P233: Store in a well-ventilated place. Keep container tightly closed.
P501: Dispose of contents/container to... (hazardous or special waste collection point)

3.2. Classification and labelling according to DSD/DPD

3.2.1. Classification and labelling in Annex I of Directive 67/548/EEC

Classification

For physicochemical properties 1,3,5-trioxane is classified as follows:
F; R11 Highly flammable

For health hazards 1,3,5-trioxane is classified as follows:
Xi; R37 Irritant, Irritating to respiratory system
Repr. Cat. 3; R36 Possible risk of harm to the unborn child

Labelling

Indication of danger:

F – highly flammable
Xn - harmful
R-phrases:
R11 - highly flammable
R37 – irritating to respiratory system
R63 - possible risk of harm to the unborn child

S-phrases:
S2 - keep out of the reach of children
S36/37 - wear suitable protective clothing and gloves
S46 – if swallowed, seek medical advice immediately and show this container or label

3.2.2. Self classification(s)

Not applicable.

3.2.3. Other classification(s)

Not applicable

4. ENVIRONMENTAL FATE PROPERTIES

4.1. Degradation

4.1.1. Abiotic degradation

4.1.1.1. Hydrolysis

The registrant submitted one key study on hydrolysis of 1,3,5-trioxane which was conducted according to OECD Guideline 111 (Hydrolysis as a Function of pH). According to this study the half-life (DT_{50}) at different pH (4, 7 and 9) was greater than 1 year.

Conclusion:
In contact with water 1,3,5-trioxane will hydrolyse slowly. This information was taken into account for hazard/risk/persistency assessment.

4.1.1.2. Phototransformation/photolysis

4.1.1.2.1. Phototransformation in air

The registrant delivered a key study where the rate constant half-life for the reaction of OH radicals with 1,3,5-trioxane was calculated as 37.5 h and this value was used for CSA. The SRC AOPWIN v1.92 program was used for the estimation.

Conclusion:
After evaporation or exposure to air, 1,3,5-trioxane will be slowly degraded by photochemical process.

4.1.1.2.2. Phototransformation in water

No experimental data available on phototransformation in water.

4.1.1.2.3. Phototransformation in soil

No experimental data available on phototransformation in soil.

4.1.2. Biodegradation

4.1.2.1. Biodegradation in water

4.1.2.1.1. Estimated data

This information is not available.

4.1.2.1.2. Screening tests

Conclusion:
According to key study on ready biodegradability presented in the registration dossier 1,3,5-trioxane is not readily biodegradable. Whereas in accordance with key study on inherent biodegradability 1,3,5-trioxane is inherently biodegradable. The test methods are appropriate.

4.1.2.1.3. Simulation tests (water and sediments)

Data waiving.

Conclusion:
The substance indicates the mobility in sediments and is inherently biodegradable. Furthermore, as the value of

log K_{oc} of 1,3,5-trioxane is equal -0.416 the substance is considered to have low adsorptive properties.

4.1.2.1.3. Summary and discussion of biodegradation in water and sediment

Conclusion:

- screening testing

In accordance with modified Zahn-Wellens study (OECD 302B) the substance degraded more than 90% of the DOC removal in 18 days. According to REACH Guidance on Information Requirements R.7b it may be regarded as evidence of inherent, ultimate biodegradability. Thus this indicates that 1,3,5-trioxane is effectively removed via biodegradation from wastewater at a treatment plant.

Easily eliminated from water - this information was taken into account for hazard/risk/persistency assessment. In CSA used information on biodegradation in water i.e. inherently biodegradable.

- simulation testing

Please refer to point 4.1.2.1.3.

4.1.2.2. Biodegradation in soil

Data waiving

Conclusion:

Direct exposure of 1,3,5-trioxane into soil is unlikely. Besides 1,3,5-trioxane is considered as mobile in soil and inherently biodegradable.

4.1.3. Summary and discussion of degradation

Conclusion:

- Abiotic degradation

Information was taken into account for hazard/risk/persistency assessment:

- 1,3,5-trioxane will hydrolyse slowly under environmental conditions (half-life > 1 yr).
- the half-life (37.5h) indicates that after evaporation or exposure to the atmosphere, the substance will be slowly degraded by photochemical processes.

- Biotic degradation

Information was taken into account for hazard/risk/persistency assessment:

- 1,3,5-trioxane is easily eliminated from water and inherently biodegradable.
- the low adsorptive properties of 1,3,5-trioxane indicates that it is considered to be mobile in sediments and soils.

4.2. Environmental distribution

4.2.1. Adsorption/desorption

Conclusion:

1,3,5-trioxane has low potential for adsorption. The log Koc of 1,3,5-trioxane was calculated using SRC PCKOCWIN v2.00 and is equal -0.416 (corresponding Koc = 2.603).

Information was taken into account for hazard/risk/persistency assessment: adsorption to solid soil phase is not expected and the value used for CSA: Koc = 2.6 L/kg at 20°C are acceptable.

4.2.2. Volatilisation

Conclusion:

The Henry's Law constant (0.57 Pa m^3/mol) and the vapour pressure (11 hPa at 20 °C) of 1,3,5-trioxane indicate that the substance is volatile.

4.2.3. Distribution modelling

Conclusion:
According to key study submitted by the registrant (calculation according to Mackay, Level I) the following distribution has been determined:
Air (%): 19.95; Water (%): 80.05; Soil (%): 0; Sediment (%): 0 (BASF AG, 2007)

4.2.4. Summary and discussion of environmental distribution

Conclusion:
The substance has low adsorption and it indicates that soil and sediment are not expected to be the main target compartments for exposure assessment. This study indicates that the substance mainly distributes into water (ca. 80%) and air (ca. 20%).

4.3. Bioaccumulation

4.3.1. Aquatic bioaccumulation

Data waiving.

Conclusion:
The bioaccumulation is not expected for 1,3,5-trioxane because the calculated log Kow of this substance is equal - 0.5.

4.3.2. Terrestrial bioaccumulation

Data waiving.

Conclusion:
Based on the information on value of log Kow (i.e. ≤3) for 1,3,5-trioxane it can be concluded that the bioaccumulation is not expected for this substance.

4.3.3. Summary and discussion of bioaccumulation

Conclusion:
Bioaccumulation of 1,3,5-trioxane in aquatic and terrestrial organisms is not expected.

4.4. Secondary poisoning

Conclusion:
No bioaccumulation properties of 1,3,5-trioxane in aquatic and terrestrial organisms indicates that the secondary poisoning study is not needed.

5. HUMAN HEALTH HAZARD ASSESSMENT

The evaluation of the toxicity of 1,3,5-trioxane has been based on data presented by the registrants (IUCLID, CSRs) and other information available in scientific literature

5.1. Toxicokinetics (absorption, metabolism, distribution and elimination)

5.1.1. Non-human information

1,3,5-trioxane was metabolized to formaldehyde with carbon dioxide and water as the final products as was shown in the key study, following i.p. injection (40 and 400 mg/kg bw, rats).
When administered orally (2500 mg/kg bw, rats) it is readily absorbed and metabolized to CO_2 and eliminated in expired air.
Furthermore, 1,3,5-trioxane is transferred via placenta to the tissues of the foetus following oral administration (40 mg/kg bw, rats).

5.1.2. Human information

No relevant human information is available.

5.1.3. Summary and discussion of toxicokinetics

The toxicokinetic study indicates that 1,3,5-trioxane is readily absorbed from the gastrointestinal tract. It is metabolized primarily to formaldehyde and is excreted mainly as carbon dioxide in exhaled air, while the minor part is excreted via urine. 1,3,5-trioxane crosses the placenta and is incorporated into foetal tissues to a greater extent than to the tissues of the mother. It is distributed mainly to the liver and to a lesser extent to the fat and brain tissues. Because it is eliminated rapidly, 1,3,5-trioxane is not expected to bioaccumulate significantly.
Inhalation of vapours is the primary route of exposure. There are no toxicokinetic studies following inhalation or skin exposure. Based on the physicochemical properties, 1,3,5-trioxane is considered as easily transported via the alveolar and capillary membranes and effectively removed from the air in the upper respiratory tract and as. 1,3,5-trioxane is poorly absorbed through the skin.

5.2. Acute toxicity

5.2.1. Non-human information

5.2.1.1. Acute toxicity: oral

The acute oral LD_{50} value in rats was greater than 2000 mg/kg bw. This value is between: 3200 mg/kg bw, and 8190 mg/kg bw depending upon the study. Details of toxic effects were not reported.

5.2.1.2. Acute toxicity: inhalation

According to the key studies submitted by the registrant the LC_{50} value in rats (4h) was greater than 39.2 mg/l. No target organs were identified at necropsy. The symptoms included secretion, respiratory distress, poor condition and reduction in body weight following exposure. Animals gained body weight during the second week of the observation period.
The supporting studies revealed LC_{50} value between > 22 mg/l (8h) and >26 mg/l (4h).

5.2.1.3. Acute toxicity: dermal

The dermal LD50 value was ranged between >3900 mg/kg bw and >15000 mg/kg bw. Slight to moderate skin irritation was observed but no classification was indicated.

5.2.1.4. Acute toxicity: other routes

Not relevant for assessment

5.2.2. Human information

No relevant human information is available.

5.2.3. Summary and discussion of acute toxicity

The data submitted by registrant is suitable for evaluation of acute toxicity of 1,3,5-trioxane. The substance is of low oral, inhalation and dermal toxicity. The classification is not required.

The following information is taken into account for any hazard / risk assessment:

Oral: LD_{50} > 3200 mg/kg for rats
Inhalation: LC_{50} = 39.2 mg/l/1 hr for rats
Dermal: LD_{50} > 3980 mg/kg for rabbits

Justification for classification or non classification
According to the classification criteria of Directive 67/548/EEC and Regulation (EC) No. 1272/2008 (CLP Regulation)1,3,5-trioxane does not require classification for acute toxicity.

5.3. Irritation

5.3.1. Skin

5.3.1.1. Non-human information

1,3,5-trioxane did not irritate the skin of rabbit in semi-occlusive and occlusive test: erythema and oedema scores = 0.

5.3.1.2. Human information

No relevant human information is available.

5.3.2. Eye

5.3.2.1. Non-human information

There are available 5 studies related to eye irritation. The results are presented in the Table 3.

Table 3. Overview of experimental studies on eye irritation

Reference	No of rabbits	Results			
		Iris	Conjunctiva	Chemosis	Cornea
Hoechst, 1989*	3	0.11	1.66	0.66	0
BASF, 1968b**	2	0.33	1.33	0.67	1
International Toxicology Service Department, 2002	6	0.23	1.67	0.73	0.63
Celanese Engineering Resins, 1986	6	Iritis in 3 rabbits	Marked conjunctivitis in 6 rabbits		Corneal opacities in 5 rabbits Corneal ulceration in 5 rabbits
Czajkowska, 1987	21	Score 58 out of 110 according to the system described by Kay and Calandra (1962)			

* key study submitted by the registrant
** supporting study submitted by the registrant

The eye irritation potential was determined by installation of 1,3,5-trioxane into the conjunctival sac of rabbits.

The test material caused moderate irritation of the conjunctive and mild chemosis. All symptoms were fully reversible after 72h of observation. The supporting study indicates mild to moderate irritation of conjunctiva, mild iritis and chemosis and corneal opacity with mean value =1 for two rabbits. According to CLP classification criteria for category 2:

"If, when applied to the eye of an animal, a substance produces:
- *at least in 2 of 3 tested animals, a positive response of:*
– *corneal opacity ≥ 1 and/or……*
calculated as the mean scores following grading at 24, 48 and 72 hours after installation of the test material and which fully reverses within an observation period of 21 days."

According to the supporting study, 1,3,5-trioxane meets the criterion as irritating to eyes. Two animals instead of a three in used in the experiment do not negate the results of this study.
There are three other studies available. The older one showed mild corneal opacity and chemosis and moderate conjunctival irritation which were reversible within 10 days. On the basis of this study classification of 1,3,5-trioxane is not needed.
In the second study the irritation score 58 out of maximum score of 110 and reversibility within 6 days indicate severe eye irritation as is indicated in modified Kay and Calandra classification system. The severe irritating potential of 1,3,5-trioxane was confirmed in another study in which the observed changes were reversible within 10 days after treatment.

The results of available studies provide a basis for classification of 1,3,5-trioxane as an eye irritant category 2, according to CLP classification criteria.

5.3.2.2. Human information

No relevant human information is available.

5.3.3. Respiratory tract

5.3.3.1. Non-human information

See 5.6.1.2 (Repeated dose toxicity: inhalation)

5.3.3.2. Human information

No relevant human information is available.

5.3.4. Summary and discussion of irritation

The data submitted by registrant for registration is suitable for evaluation of skin and eye irritation. Based on the data it can be concluded that 1,3,5-trioxane is not irritant to the skin but it is irritant to the eyes.

The substance is irritating for respiratory tract (See 5.6.1.2 (Repeated dose toxicity: inhalation).

The following information is taken into account for any hazard / risk assessment:
Skin irritation: not irritant
Eye irritation: irritant
Respiratory irritation: irritant

Justification for classification or non classification
According to the classification criteria of Directive 67/548/EEC and Regulation (EC) No. 1272/2008) 1,3,5-trioxane does not require classification for skin irritation, but requires classification for eyes irritation. Due to signs of local respiratory tract irritation following repeated inhalation exposure, 1,3,5-trioxane is classified as: Directive 67/548/EEC: R37; CLP Regulation: $STOT_{single}$ category 3 (H335, may cause respiratory irritation).

5.4. Corrosivity

5.4.1. Non-human information

See Section 5.3

5.4.2. Human information

See Section 5.3

5.4.3. Summary and discussion of corrosion

See Section 5.3

5.5. Sensitisation

5.5.1. Skin

5.5.1.1. Non-human information

A maximization test which was carried out in guinea pigs showed that 1,3,5-trioxane had no sensitizing properties. The older studies gave a negative result regarding sensitizing potential of 1,3,5-trioxane.

5.5.1.2. Human information

The study with dentists, dental technicians and specialist auxiliary staff with contact eczema revealed one case of trioxane allergy (1.2% of all patients studied.
Another older study carried out in dental students showed an allergic potential in 28.8% of studied persons.

5.5.2. Respiratory system

5.5.2.1. Non-human information

No information is available

5.5.2.2. Human information

No information is available

5.5.3. Summary and discussion of sensitisation

The data submitted by registrant is suitable for evaluation of the skin sensitization. Based on this data1,3,5-trioxane can be concluded as not sensitizing for the skin. Still because trioxane degradation results in the release of small amounts of formaldehyde which is a well-known human skin sensitizer and from this perspective possible implications for formaldehyde-susceptible individuals should be indicated in the hazard communication (MSDS).

The following information is taken into account for any hazard / risk assessment:

Skin sensitization: not sensitizing

Justification for classification or non classification

According to the classification criteria of Directive 67/548/EEC and Regulation (EC) No. 1272/2008) 1,3,5-trioxane does not require classification for skin sensitization.

5.6. Repeated dose toxicity

5.6.1. Non-human information

5.6.1.1. Repeated dose toxicity: oral

1,3,5-trioxane when administered orally at a dose of 30, 100 and 300 mg/kg bw for 90 days produced no adverse effects in the highest dose level. Slight changes as an early sign of reduced erythropoiesis and disturbance in iron metabolism were observed in high dose males. Therefore the value of 300 mg/kg bw was identified as NOAEL.
In an earlier 4-week study the rats received 1,3,5-trioxane at a dose of 40, 200 and 1000 mg/kg. The behaviour and the general physical condition of the rats were normal. Haematological examination at the end of the treatment revealed significant reductions in leucocyte counts in males and females of the highest dose group. The increase in the activity of some enzymes (glutamyl transpeptidase and glutamic transaminases) was also observed in females of the top dose group. Therefore the value of 200 mg/kg bw was identified as NOAEL. The LOAEL was 1000 mg/kg bw.
According to the two other studies, the rats were exposed to 1,3,5-trioxane at different dose levels (females: 190, 580 and 1160 mg/kg bw, 7 weeks; males: 850 and 1700 mg/kg bw). In all treated females reversible behavioural changes and a dose-dependent decrease of body weight were observed. In all treated males body weight gain was decreased and weights of liver, kidney and spermatic vesicle were increased. The changes were reversible.

5.6.1.2. Repeated dose toxicity: inhalation

The repeated exposure of rats to 1,3,5-trioxane (6 hours per day, 5 days per week, 2 weeks) at the concentration of 0.38, 3.62 or 18.18 mg/l resulted in signs of respiratory irritation in all exposed groups (increased secretory responses). In the high dose group respiratory impairment and histopathologically squamous metaplasia with necrosis and desquamation of the mucosa of the anterior nasal cavity was observed. The signs of systemic toxicity observed in the high dose group only included: slight decrease of mean body weight, changes in hematological parameters (e.g. increased hemoglobin, hematocrit and erythrocyte counts, decreased leucocyte counts), changes in clinical chemical parameters (e.g. increase in serum GPT, total protein and albumin, decrease in glucose.
Based on this study a systemic NOAEC of 3.62 mg/L can be determined.
According to the supporting study on rats exposed to 1,3,5-trioxane at dose of 0.05, 0.5 and 2.5 mg/l (5 hours per day, 5 days per week, 12 months) signs of respiratory tract irritation (e.g. increased lymphocyte infiltration, tissue proliferation, metaplasia) were observed at the high dose level.

5.6.1.3. Repeated dose toxicity: dermal

Data waiving
The data on repeated dose toxicity dermal is waived.

5.6.1.4. Repeated dose toxicity: other routes

This information is not available

5.6.2. Human information

No available information

5.6.3. Summary and discussion of repeated dose toxicity

Conclusion

The data submitted by registrant is suitable for evaluation of the repeated dose toxicity. Inhalation exposure is the most appropriate route for assessing occupational risk in humans. When comparing the 28-day key studies for both tested exposure routes (oral, inhalation), a good correlation in terms of target organ toxicity (e. g. hematopoetic system) was observed. 1,3,5-trioxane is irritating for respiratory tract.

The following information is taken into account for any hazard / risk assessment:

In a 90 day gavage study no adverse signs of toxicity were observed in rats treated in the highest tested dose level (NOAEL 300 mg/kg bw/day).
In a 2 week inhalation study with rats, signs of respiratory irritation were observed in all exposed groups. Though no signs of systemic toxicity were observed.

Value used for CSA (inhalation - systemic effects):

NOAEC: 3.62 mg/m³ (subacute; rat)
Target organs: respiratory: nose

Justification for classification or non classification

According to Directive 67/548/EEC and the Regulation (EC) 1272/2008, no classification for systemic toxicity following repeated exposures is appropriate. Due to local irritation of the respiratory tract, the R37 is appropriate according to Directive 67/548/EEC or STOT Cat. 3, according to Regulation (EC) 1272/2008.

5.7. Mutagenicity

5.7.1. Non-human information

5.7.1.1. In vitro data

The available in vitro genotoxicity studies were negative. 1,3,5-trioxane was negative in a chromosomal aberration test on Chinese hamster lung fibroblast. No mutagenicity was observed in bacterial reverse mutation assay on Salmonella typhimurium with or without metabolic activation.

5.7.1.2. In vivo data

The available in vivo genotoxicity studies were negative. No genotoxicity was observed in micronucleus assay and dominant lethal assay. 1,3,5-trioxane caused no increase in unscheduled DNA synthesis in an in vivo UDS assay.

5.7.2. Human information

5.7.3. Summary and discussion of mutagenicity

1,3,5-trioxane proved not to be mutagenic in prokaryotes when tested for gene mutation in bacterial reverse mutation assay and in mammalian cell gene mutation assay. In vivo, a micronucleus test, dominant lethal assay and UDS assay indicated no mutagenic effect.

The following information is taken into account for any hazard / risk assessment:

Mutagenicity: not mutagenic in bacterial reverse mutation assay and in mammalian cell gene mutation assay.

Value used for CSA (inhalation - systemic effects):

Genetic toxicity: negative

Justification for classification or non classification

No classification for genetic toxicity indicated according to Directive 67/548/EEC and Regulation (EC) 1272/2008.

5.8. Carcinogenicity

5.8.1. Non-human information

5.8.1.1. Carcinogenicity: oral

Relevant information is not available.

5.8.1.2. Carcinogenicity: inhalation

Relevant information is not available.

5.8.1.3. Carcinogenicity: dermal

Relevant information is not available.

5.8.1.4. Carcinogenicity: other routes

Relevant information is not available.

5.8.2. Human information

In vitro, a cell transformation test was carried out. Cultures of 300 cells were incubated with trioxane concentration of: 0, 10, 100, 500, 1000, 5000, 10000 and 20000 µg/ml for 24 hours. No evidence of transformation was observed for the cell colonies.

5.8.3. Summary and discussion of carcinogenicity

Data waiving

There is no evidence from the repeated dose studies that the substance is able to induce hyperplasia and/or pre-neoplastic lesions.

Discussion

No results are available from carcinogenicity studies in experimental animals. In vitro study revealed no evidence of the cell transformation. As no indications of carcinogenic potential were described, further chronic testing regarding this endpoint is not recommended from a scientific point of view and by means of animal welfare.
The following information is taken into account for any hazard / risk assessment:

Negative in genotoxicity assays, carcinogenicity and cell transformation assay.

Value used for CSA:

Carcinogenicity: not carcinogenic

Justification for classification or non classification

No classification for carcinogenicity indicated according to Directive 67/548/EEC and Regulation (EC) 1272/2008.

5.9. Toxicity for reproduction

5.9.1. Effects on fertility

5.9.1.1. Non-human information

In a study conducted to assess the impact of 1,3,5-trioxane on fertility, male rats were administered orally to the substance at the doses of: 0, 850 or 1700 mg/kg bw (5 days/week for 8 weeks). A further study was carried out in males exposed by inhalation to the concentration of 2500 mg/m^3 (5h/day, 5 days/week for 12 months). One male was mated with 2 females for one week. Necropsy of the pregnant females was performed 13 and 14 days after the middle of mating interval. No increase in the number of pre-implantation loses and dead implants were noted in any treated group. Trioxane had no effect on the fertility of the males, although microscopic examination of the testes of some treated males revealed focal necrosis of the seminisferous tubular epithelium and alteration of spermatogenesis.
In order to determine the effect of trioxane on the measured oestrus cycle of the rat, female rats were orally treated with trioxane at the doses of: 0, 190, 580 and1160 mg/kg bw (5days/week for 7 weeks). A significant increase in the mean duration of the oestrus cycle was noted in the 6th and 7th week of treatment in females given at the highest dose of the substance.

5.9.1.2. Human information

No relevant human information is available.

5.9.2. Developmental toxicity

5.9.2.1. Non-human information

The teratogenic potential of 1,3,5-trioxane was investigated following oral administration of the substance to pregnant rats at the doses of: 0, 100, 315 or 1000 mg/kg bw. On day 21 of gestation the dams were sacrificed and necropsied. Treatment with trioxane caused no mortality or clinical signs of toxicity in the dams. In the top dose group, foetal body weight and length were decreased, while placental weight was increased. Morphological examination of the foetuses of the highest exposed group revealed two cases of aplasia of the tail accompanied by aplasia of the sacral vertebral arches and centres and the caudal vertebral centres. The incidence of foetuses with bone defects was increased in this dose group. In addition, retarded ossification was observed in various bones. The foetuses from the intermediate dose group also showed increased incidences of wavy and thickened ribs and retarded ossification.
In order to investigate the prenatal toxicity of trioxane, the pregnant rats were administered by oral gavage with doses of: 0, 770, 1550 or 3870 mg/kg/bw. No animals died during the study. The placentas of dams from all exposed groups displayed changes: fibrin deposits, inflammatory infiltrations and focal necrosis. In all treated groups the number of resorption increased in dose-dependent manner and there was also reduction in foetal body weight and length. The dose levels of 770 and 1550 mg/kg/bw gave rise to malformations of the brain, the kidneys and the skeletal system and increased the number of foetuses with delayed ossification. The potential contribution of formaldehyde to the observed effects was excluded by the authors.
A study on the reproductive toxicity of 1,3,5-trioxane investigated the postnatal development of the offspring of rats treated with the substance during pregnancy. Groups of pregnant rats were administered by gavage at 190, 580 or 1160 mg/kg/bw of trioxane. None of the dams died or showed clinical signs of toxicity. The rats treated at the highest dose level exhibited a significant reduction in litter size. Over 90% of the pups that were born died, in most cases within the first 4 days of life and hence no further assessment were carried out at that dose level. The two lower dose groups showed no effects on litter size or developmental of pups. At 580 mg/kg bw trioxane reduced motor activity in pups. When tested for active avoidance acquisition these animals showed a significant decrease in responsiveness.

5.9.2.2. Human information

No relevant human information is available

5.9.3. Summary and discussion of reproductive toxicity

High doses of 1,3,5-trioxane (oral administration) result in foetal lethality, retarded foetal growth and congenital malformations in the foetuses. The increased number of resorptions decreased foetal body weight and length and malformations of the foetal brain and skeletal system (delayed ossification) was noted following exposure to high dose of trioxane. Other effects include changes such as aplasia of the tail and the vertebral column or wavy and thickened ribs. The litter size was significantly reduced. The pups showed reduced motor activity and decrease in responsiveness in active avoidance test. No maternal toxicity was observed upon oral treatment of pregnant rats but the administration of high dose of trioxane resulted in prolongation of the oestrus cycle, mainly of the dioestrus phase which was reversible 4-5 weeks after exposure.

The following information is taken into account for any hazard / risk assessment:

Fertility: The available data do not indicate effects on fertility.
Developmental toxicity: Malformations of the fetal organs (brain and skeletal system, aplasia of the tail and the vertebral column or wavy and thickened ribs), reduced litter size.

Justification for classification or non classification

According to the classification criteria of Directive 67/548/EEC and Regulation (EC) No. 1272/2008 due to signs of developmental toxicity, 1,3,5-trioxane is classified as: EU: Repr. Cat. 3, R63 (Possible risk of harm to the unborn child); CLP: Repr. 2 (H361d: May damage the unborn child).

5.10. Other effects

5.10.1. Non-human information

No relevant information is available.

5.10.1.1. Neurotoxicity

Behavioural changes observed in rat offspring following maternal exposure to 1,3,5-trioxane (reduced locomotor activity and decrease of active avoidance acquisition) may be related to neurotoxicity.

5.10.1.2. Immunotoxicity

No relevant information is available.

5.10.1.3. Specific investigations: other studies

No information is available

5.10.2. Human information

No information is available

5.10.3. Summary and discussion of other effects

This information is not available.

5.11. Derivation of DNEL(s) and other hazard conclusions

5.11.1. Overview of typical dose descriptors for all endpoints

Acute toxicity oral : LD50 > 2000 mg/kg
Acute toxicity dermal : LD50 > 2000 mg/kg
Acute toxicity inhalation (rats): LC50 > 39.2 mg/l
Irritation /Corrosivity-skin: not irritating
Irritation /Corrosivity-eye: the results of available studies provide a basis for classification as an eye irritant
Irritation /Corrosivity-respiratory tract: irritating
Sensitisation skin: not sensitising
Sensitisation respiratory tract: not sensitising
Repeated dose toxicity: sub-acute / sub-chronic / chronic-inhalation: NOAEC: 3.62 mg/m^3 (subacute). Target organs: respiratory: nose
Mutagenicity: not mutagenic
Carcinogenicity: not carcinogenic
Reprotoxicity: reprotoxic

5.11.2. Selection of the DNEL(s) or other hazard conclusion for critical health effects

Table 4. Hazard conclusions for workers

Route	Type of effect	Hazard conclusion	Most sensitive endpoint
Inhalation	Local effects - Acute	DNEL: 20 mg/m³	irritation (respiratory tract)
Inhalation	Systemic effects – Long-term	DNEL: 24 mg/m³	repeated dose toxicity

Route	Type of effect	Hazard conclusion	Most sensitive endpoint
Inhalation	Local effects – Long term	DNEL: 10 mg/m³	irritation (respiratory tract)
Dermal	Systemic effects – Long-term	DNEL: 3.0 mg/kg/bw/day	repeated dose toxicity

Table 5. Hazard conclusions for general population

Route	Type of effect	Hazard conclusion	Most sensitive endpoint
Inhalation	Systemic effects – Long-term	DNEL: 6.0 mg/m³	repeated dose toxicity
Oral	Systemic effects – Long-term	DNEL: 0.5 mg/kg/bw/day	repeated dose toxicity

Discussion

DNELs for workers

Due to the type of use of 1,3,5-trioxane, inhalation and dermal exposure plays an important role in industrial environment.

The following DNELs were derived:

- Acute – local effects: inhalation: 20 mg/m^3. To obtain a ceiling limit value for acute effects at the portal of entry the $DNEL_{inhal.}$, local, chronic of 10mg/m^3 can be extrapolated with a factor of 2.
- Long-term – systemic effects: dermal: 3 mg/kg/bw. As no data on long term inhalation exposure is available the value was derived on the basis of long-term oral exposure (13 week). The corrected NOAEL was 300 mg/kg/bw (reduced erythropoiesis and disturbance in iron metabolism). After applying the relevant assessment factors, a DNEL value of 3 mg/kg/bw day was derived.
- Long – term – systemic effects: inhalation. Inhalatory NOAEC of 3620 mg/m^3 was derived on the basis of 2 weeks inhalation study (effects on hematopoietic system and biochemical parameters). After applying the relevant assessment factors, a DNEL value of 24 mg/m^3 was derived.
- Long – term – local effects: inhalation. The starting point for calculation DNEL was LOAEC of 375 mg/m^3 (established on 2 week inhalation study). After applying the relevant assessment factors, a DNEL value of 10 mg/m^3 was derived.
-

The following DNELs / DMELs were not derived:

- Acute - systemic effects: dermal and inhalation. Trioxane is not classified for acute systemic effects. Thus, the derivation of the respective DNEL is not required.
- Acute – local effects: dermal. Trioxane is not classified for skin/eye irritation and skin sensitisation. Thus, the derivation of the respective DNEL is not required.
- Long-term - local effects: dermal. Trioxane is not classified for local effects including skin/eye irritation and skin sensitisation. Thus, the derivation of the respective DNEL is not required.

DNELs for the general population

As the substance is not used by the general population, only the DNELs needed for assessing the risk of the substance from indirect exposure via the environment are derived.

The following DNELs were derived:

- Long – term systemic effects, inhalation. The DNEL value of 6 mg/m^3 was set on the basis of NOAEC=3.62 g/l, using relevant safety factors.
- Long – term, systemic effects, oral. The DNEL value of 0.5 mg/kg/bw/day was set on the basis of NOAEL=300 mg/kg/bw/day, using relevant safety factors.

The registrant submitted the correct calculation of DNELs related to the relevant routes of exposure and according to the Guidance of information requirements and chemical safety assessment. Chapter R.8: Characterisation of dose [concentration]-response for human health (2012).

6. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICOCHEMICAL PROPERTIES

6.1. Explosivity

1,3,5-trioxane has no chemical groups associated with explosive properties. It is not explosive.

The following information is taken into account for any hazard/risk assessment:
Not explosive.

6.2. Flammability

Flammability
1,3,5-trioxane is highly flammable. Flammability was derived from burning time test (UN). According to study by BASF AG (2001), burning time for the substance is 3-5 sec.
Based on chemical structure pyrophoric properties and flammability in contact with water are not to be expected.

The following information is taken into account for any hazard / risk assessment:
Highly flammable.
The substance has no pyrophoric properties and does not liberate flammable gases on contact with water.

Flash point

The flash point does not need to be tested as the substance is a solid.
The following information is taken into account for any hazard / risk assessment:
Not applicable.

Classification according to GHS

Name: 1,3,5-trioxane
State/form of the substance: solid
Classification (Flammable solids): Flam. Solid 1 (Hazard statement: H228: Flammable solid.)
Reason for no classification (Flammable gases): data lacking
Reason for no classification (Flammable aerosols): data lacking
Reason for no classification (Flammable liquids): data lacking

Classification according to DSD / DPD

Classification status: 67/548/EEC annex 1 (1,3,5 Trioxane)
Classification: F; R11 Highly flammable; Highly flammable
Justification for classification or non-classification:
Burning time is <45s, and wetted zone does not stop fire. ---> GHS classification criteria for flammable solids: Category 1

6.3. Oxidising potential

The oxidizing properties of the substance do not need to be tested because the substance is highly flammable.

The following information is taken into account for any hazard / risk assessment:
No oxidising properties.

Classification according to Regulation (EC) No 1272/2008
Name: 1,3,5-trioxane
State/form of the substance: solid
Reason for no classification (Oxidising gases): data lacking
Reason for no classification (Oxidising liquids): data lacking
Reason for no classification (Oxidising solids): conclusive but not sufficient for classification

7. ENVIRONMENTAL HAZARD ASSESSMENT

7.1. Aquatic compartment (including sediment)

7.1.1. Fish

7.1.1.1. Short-term toxicity to fish

The registrant submitted three acute toxicity studies on fish for 1,3,5-trioxane, all with Klimisch Code 2. In two studies freshwater species were used. In the third one there was used saltwater species. The results of all studies show law acute toxicity of 1,3,5-trioxane for fish.
According to the key study, static one, using Leuciscus idus for test the LC50 (96h) of approximately 4000mg/L and a NOEC (96h) of 2150 mg/L was reported. In another study, flow through one, where freshwater species Pimephales promelas was used a LC50 (96h) of 5950 mg/L was reported. This one was presented as supporting study.
In a non GLP study and non-guideline marine study with Cyprinodon variegatus a LC50 (96h) of 16350 mg/L was reported.

Comment

The registrant choose as the key study acute test with Leuciscus idus where LC50(96h) value was approximately 4000 mg/L. On the basis of this study the registrant concluded that 1,3,5-trioxane is not acute harmful to fish. As supporting study there was used study on marine fish, where LC50(96h) value was 16350 mg/L.
Analysing further details regarding the key study that was available for evaluator from additional source of information, there should be mentioned that the key study was performed along with the *German standard guideline DIN 38412, part 1*5. In this source of information was also said that study closely followed the OECD 203 guideline with the exception of choice of species for test, different than recommended by the current OECD method[1]. On the basis of additional information there can be also clarified that the key study **was not conducted with accordance to GLP standards**, although the registrant considered it as GLP study.
Taking into account all available information it can be concluded that the registrant choose the correct study as the key one, in spite of the lack of GLP compliance. It can be confirmed that 1,3,5- trioxane shows low acute toxicity to fish.

LC50 for freshwater fish (96h): 4000 mg/L
LC50 for saltwater fish (96h): 16350 mg/L

7.1.1.2. Long-term toxicity to fish

No data on long-term toxicity to fish was provided. The registrant used data waiving justifying this fact with provisions laid down in Annex IX of Regulation (EC) No 1907/2006. On the basis of these provisions long-term toxicity to fish shall be proposed by registrant if the chemical safety assessment indicates the need to investigate further the effects on fish. According to Annex I of this regulation, the chemical safety assessment triggers further actions when the substance or preparations meets the criteria for classification as dangerous according to Directive 67/548/EEC or Directive 1999/45/EC or is assessed to be a PBT or vPvB. The registrant summarized that the hazard assessment of 1,3,5-trioxane showed neither a need to classify the substance as dangerous to the environment, nor meeting the criteria for PBT or vPvB substance, nor further indications that the substance may be hazardous to the environment. Furthermore, the registrant invokes the results of modelling. EpiWin v4,00 EcoSAR v 1.00 calculation was conducted to estimate the chronic toxicity to fish. The result of this calculation showed no chronic toxicity to fish (ChV>1000 mg/L).
On the basis of all available information, the registrant concluded that with high probability 1,3,5-trioxane has no chronic effect to fish.

Comment

[1] *1,3,5-TRIOXANE USEPA* HPV Challenge Program Submission; December X, 2000, p. 44 and 46

1,3,5-trioxane is not classified as dangerous for environment and does not fulfil the criteria for PBT or vPvB. On the basis of these arguments, it can be agreed that conclusion of the registrant, that with highly probability 1,3,5-trioxane has no chronic effects to fish, is correct. Consequently, there is no concern for long-term toxicity to fish.

7.1.2. Aquatic invertebrates

7.1.2.1. Short-term toxicity to aquatic invertebrates

The registrant submitted two studies on acute toxicity to aquatic invertebrates. Both of them are with Klimisch Code 2.
The key study, done by Fraunhofer Institute (1989), reported no toxicity to Daphnia magna in the highest tested concentration of 1000 mg/L what means that EC50(48h) was greater than this value. The second study, supporting one, where Daphnia magna was used as well, determined a LC50(48h) of 15200 mg/L. On the basis of these results the registrant concluded that with high probability 1,3,5-trioxane is not acute harmful to aquatic invertebrates.

Comment

According to the additional source of information, that are available for evaluator, the study chosen by the registrant as the key one, followed the OECD 202 guideline. However, it could not be determined if the study was conducted with accordance to GLP standards. Study design and reporting meets current OECD guideline with minor exceptions. [2]
Taking into account information given by registrant and details from additional source of information it can be agreed that conclusion of the registrant, that with highly probability 1,3,5-trioxine has no acute harmful effects to aquatic invertebrates, is correct. Consequently it can be concluded, that 1,3,5- trioxane shows low acute toxicity to aquatic invertebrates and there is no need for further tests.
EC50 for freshwater invertebrates: > 1000 mg/L

7.1.2.2. Long-term toxicity to aquatic invertebrates

No data on long-term toxicity to aquatic invertebrates was provided. On the basis of these provisions long-term toxicity to aquatic invertebrates shall be proposed by the registrant if the chemical safety assessment indicates the need to investigate further the effects on aquatic invertebrates. According to Annex I of this regulation, the chemical safety assessment triggers further actions when the substance or preparations meets the criteria for classification as dangerous according to Directive 67/548/EEC or Directive 1999/45/EC or is assessed to be a PBT or vPvB. The registrant summarized that the hazard assessment of 1,3,5 trioxane showed neither a need to classify the substance as dangerous to the environment, nor meeting the criteria for PBT or vPvB substance, nor further indications that the substance may be hazardous to the environment.

Comment

1,3,5-trioxane is not classified as dangerous for environment and does not fulfil the criteria for PBT or vPvB. On the basis of these arguments, it can be agreed that with highly probability 1,3,5-trioxine has no chronic effects to aquatic invertebrates is correct.

7.1.1.3. Algae and aquatic plants

The registrant submitted two studies on acute toxicity to aquatic plants. Both of them are with Klimisch Code 2.
The key study, performed according to EU methods (EG-guideline 88/302/EWG, Annex V, C: Algal inhibition test) showed no effect on aquatic algae up to the highest test concentration of 500 mg/L after 72 h of exposure. In the second study submitted by the registrant as supporting one there was determined NOEC greater than 5000 mg/L.
On the basis of these results the registrant concluded that with high probability 1,3,5-trioxane is not acute harmful to aquatic algae.

[2] *1,3,5-TRIOXANE USEPA* HPV Challenge Program Submission; December X, 2000, p. 49

Comment

Toxicity to aquatic plants was evaluated in two studies. The first, key study, measured the growth rate of Scenedesmus subspicatus in the presence of 1,3,5-trioxane at concentrations up to 500 mg/l and determined the EC50 greater than 500 mg/l. In the supporting study 1,3,5-trioxane was tested for growth inhibition of Selenastrum capricornutum. This study allowed to establish NOEC value that was greater than 5000 mg/l.
On the basis of additional sources of information there can be confirmed that key study was not conducted with accordance to GLP standards, however study design and reporting meets current OECD guideline with minor exceptions[3].
Taking into account information given by registrant and details from additional source of information it can be agreed that conclusion of the registrant, that with highly probability 1,3,5-trioxine has no acute harmful effects to aquatic algae, is correct. Consequently it can be concluded, that 1,3,5- trioxane shows low acute toxicity to algae and aquatic plants and there is no concern.
EC50 for freshwater algae: 500 mg/L

7.1.1.4. Sediment organisms

The registrant used data waiving justifying this fact with physicochemical data which indicate that 1,3,5-trioxane is not very adsorptive (log Koc = -0,416) or bioacumulative (log Pow = -0,5) a relevant distribution into the sediment organisms is not expected.

Comment

1,3,5-trioxane has low adsorptive and bioaccumulative properties. A significant distribution into the sediment compartment and a considerable exposure of sediment organisms is not expected.

7.1.2. Calculation of Predicted No Effect Concentration (PNEC)

7.1.2.1 PNEC water

The calculation of PNEC fresh and marine water was based on the results for the toxicity of 1,3,5-trioxane to the most sensitive specious. The registrant choose, in both cases, the assessment factors that are conservative and protective and are design to ensure that substances with the potential to cause adverse effects are identified in the hazard assessment. The registrant derived also PNEC water for intermittent releases, where the LC50 for the most sensitive specious was chosen and assessment factor 100.

Comment

The registrant used for the derivation of PNEC for fresh and marine water, as well as for derivation of PNEC for intermittent release, the results of LC50 derived in the toxicity tests for most the most sensitive specious. The choice of LC50 values and assessment factors, used for PNEC's calculations was correct.

7.1.2.2 PNEC sediment

Comment

According to information submitted in CSR PNEC for sediment is calculated using equilibrium partitioning. The registrant submitted the table with PNEC sediment calculation. However, it is not clear from which study are the data presented in the table and the way of calculating the PNEC.
In the discussion on sediment organisms the registrant used the data waiving that was justified by physicochemical data which indicates that substance is not very absorptive or bioaccumulative. What is more, in the discussion on this issue the registrant informed that there was not available information concerning effects on sediment organisms (see Chapter 7.1.1.4.).
Taking into account information on environmental fate properties of 1,3,5-trioxane especially the results determined during modelling of distribution of 1,3,5-trioxane, the discussed substance is not distributed to soil and to sediment (see Chapter 4.2.3). Furthermore, the substance is not expected to bioaccumulate see Chapter 4.3) and due to the low adsorptive properties trioxane is considered to be mobile in sediments and soils and both compartments are not expected to be the main targets for exposure assessment.

[3] *1,3,5-TRIOXANE USEPA* HPV Challenge Program Submission; December X, 2000, p. 52

Thus the information on calculation of PNEC for sediment is needed just for clarification on method used.

Taking into account information above the clarification of the chapter 7.1.2.2., regarding the PNEC is desirable to be done by the registrant in updated dossier.

7.2. Terrestrial compartment

7.2.1. Toxicity test results

No data was provided. The substance shows a low adsorptive (log Koc = -0.416) as well as a low bioaccumulative (log Pow = -0.5) potential. Thus, a significant distribution into soil and a considerable exposure of terrestrial organisms is not expected.

Comment

No data was provided. It is reasonable not to expect a significant distribution of the substance into the soil and consequently not to expect exposure of terrestrial organisms. It is worth mentioning that direct exposure of soil to the 1,3,5-trioxane is unlikely (see point 4.1.2.2).
A relevant exposure of soil macroorganisms, terrestrial arthropods, terrestrial plants and soil microorganisms is not expected, therefore there is no need for further testing.

7.2.2. Calculation of Predicted No Effect Concentration (PNEC soil)

7.2.2.1. PNEC soil

7.1.2.2 PNEC sediment

Comment

According to information submitted by the registrant, PNEC for soil is calculated using equilibrium partitioning. The registrant submitted the table with PNEC soil calculation. However, it is not clear from which study are the data presented in the table and the way of calculating the PNEC.
In the discussion on terrestrial compartment the registrant used the data waiving for every endpoint that was justified by physicochemical data which indicates that substance is not very absorptive or bioaccumulative. What is more, in the discussion on this issue the registrant informed that there was not available information concerning effects on soil compartment (see Chapter 7.2).
Taking into account information on environmental fate properties of 1,3,5-trioxane especially the results determined during modelling of distribution of 1,3,5-trioxane, the discussed substance is not distributed to soil and to sediment (see Chapter 4.2.3). Furthermore, there is not expected bioaccumulation of the substance (see Chapter 4.3) and due to the low adsorptive properties trioxane is considered to be mobile in sediments and soils and both compartments are not expected to be the main targets for exposure assessment.

In view of information above, the clarification of the chapter 7.2.2., regarding the PNEC for soil is desirable to be done by the registrant in updated dossier.

7.3. Atmospheric compartment

No information is available.

7.4. Microbiological activity in sewage treatment system

7.4.1. Toxicity to aquatic micro-organisms

The inhibition of the degradation activated sludge is not anticipated when introduced in an appropriate low concentration.
The lead-registrant estimates a PNEC of 9.8 mg/L for sewage treatment plant, based on the results for the toxicity of 1,3,5-trioxane to activated sludge (EC10 = 98 mg/L) and using an Assessment Factor of 10.

7.5. Non compartment specific effects relevant for the food chain (secondary poisoning)

Due to low LogPow (-0.5) and low adsorptive (-0.416), significant accumulation in organisms is not expected. Therefore, secondary poisoning is of no concern for 1,3,5-trioxane and no PNEC is derived.

7.6. Conclusion on the environmental hazard assessment and on classification and labelling

Environmental classification justification

The registrant summarised that the classification of 1,3,5-trioxane according to either Annex VI of Directive 67/548/EEC or GHS classification (GHS UN rev.2, 2007) is: no need for labelling "environment".

Summarizing data presented by the registrant it can be concluded that 1,3,5-trioxane does not fulfil criteria of classifying the substance and dangerous for the environment lied down in the Directive 67/548/EEC and Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006.

8. PBT AND vPvB ASSESSMENT

8.1. Assessment of PBT/vPvB Properties

8.1.1. PBT/vPvB criteria and justification

8.1.2. Summary and overall conclusions on PBT or vPvB properties

In accordance to the certain provisions of regulation REACH, substances that fulfil the PBT/vPvB criteria are Substances of Very High Concern (SVHC) and are subject to authorisation (Title VII of the REACH Regulation). The PBT and vPvB assessment is one of the elements of a Chemical Safety Assessment (CSA). The objective of the PBT and vPvB assessment is to determine if a substance fulfils the criteria for the identification of PBT and vPvB substances given in Annex XIII and if so, to characterise the potential emission of the substance.

As a minimum the data specified in Annex VII should be available, i.e. data comprising:
1. Degradation (ready biodegradability and/or hydrolysis)
2. Bioaccumulation (octanol/water coefficient, log Kow), and
3. Toxicity (human and aquatic toxicity)

A PBT assessment is preferably based on experimental data on the substance for biodegradation, bioaccumulation and aquatic toxicity. The identification of fulfilment of the PBT/vPvB criteria is done in a stepwise approach, which is outlined below.

Persistence (P) criterion

In order to be able to assess whether a substance is a PBT/vPvB substance, it is required that its degradability has been studied in a simulation test where half-life in water, sediment and/or soil is determined under environmentally relevant conditions.

Results
A modified test on ready degradation and test on inherent biodegradation are available. The results of these studies indicate slow to negligible biodegradation of 1,3,5-trioxane.

Conclusion for the P criterion
The substance is expected to be persistent in the environment and it is identified as potentially P.

Bioaccumulation (B) criterion

A substance has a potential to bioaccumulate if it is readily accessible for uptake by organisms, and is only slowly metabolised or excreted. The rate of substance's bioaccumulation is indicated by the bioaccumulation factor (BAF), which is obtained by relating the concentration in the organisms at equilibrium to the concentration in the surrounding environment and in food. BAF is often replaced in practice by bioconcentration factor (BCF), where the concentration in the organisms is only related to the concentration in the surrounding environment, which is experimentally easier to determine.

Results
A bioconcentration factor of 3.2 was estimated for 1,3,5-trioxane. The value is below of 4.5 indicating that this chemical is not bioaccumulative.

Conclusion for the B criterion

1,3,5-trioxane is not bioaccumulative based on the experimental log Kow of 3.2 and is therefore identified as not potentially B.

Toxicity (T) criterion
The toxicity of a substance should be assessed on the basis of chronic or long-term ecotoxicity data or CMR or chronic toxicity assessment.
If the substance is classified as carcinogenic (category 1A or 1B), mutagenic (category 1A or 1B), or toxic for reproduction (category 1A, 1B or 2) or toxic following repeated exposure it is considered toxic.

Results
The assessment of CMR properties resulted in classification of 1,3,5-trioxane as a substance toxic for reproduction (CMR Cat.2, H361d – may damage the unborn child).

Conclusion for the T criterion
1,3,5-trioxane is classified as reprotoxic according to CLP Regulation. Based on the classification the substance fulfils T criteria, therefore 1,3,5-trioxane is indicated as potentially T.

Overall conclusion
Regarding the available data it can be stated that 1,3,5-trioxane is persistent in the environment, has low bioaccumulation potential and it is toxic therefore 1,3,5-trioxane meets the criteria as a substance persistent in the environment (P) and toxic (T) but does not meet the criteria for bioaccumulation (B).
According to the guidance on PBT assessment (R.11, 2012), substances are considered as PBT (or vPvB) when they fulfill the criteria for all three (or two) inherent properties P, B an T (or vP and vB). As 1,3,5-trioxane does not fulfill B criterion it is not PBT substance.

8.2. EMMISSION CHARACTERISATION

This section is not relevant for the evaluation.

9. EXPOSURE ASSESSMENT

Table 6. Relevant substance information used in the exposure assessment

Substance	**1,3,5-trioxane**
CAS number	110-88-3
EC-number	203-812-5
Molecular weight range	90.0779
Physical state	Solid
Melting point	62 °C
Boiling point	115 °C
Relative density at 20 °C	1.39 g/cm^3
Vapour pressure at 20 °C	11 hPa
Partition coefficient at 25 °C	-0.5
Water solubility at 20 °C	172 g/l

9.1 Introduction and uses

Nine Chemical Safety Reports are available in IUCLID. The CSRs are different regarding the identified uses.

1,3,5-trioxane has been registered by nine companies According to two companies risk characterization is not necessary as the substance manufactured outside the EU was imported as part of polymers only. In the table below uses identified by the lead registrant are presented.

Table 7. Identified uses of 1,3,5-trioxane

Uses by workers in idustrial settings
Manufacturing of 1,3,5-trioxane
Polymerization of 1,3,5-trioxane
Use of the substance as laboratory chemical

Worker exposure

1,3,5-trioxane is manufactured in the EU or outside the EU and is imported into EU. Most of this amount is also used by the registrant, at the same site.
Due to relatively high vapour pressure of 1,3,5-trioxane, there is a high concern for potential risk to workers.
The exposure of workers have been calculated using ECETOC TRA v.2 tool. Exposure to the liquid form has been used due to the high vapour pressure and in order to take account formation of vapour. The substance is classified as irritating to the respiratory tract, therefore the Risk Management Measures of wearing respiratory protection and using Local Exhaust Ventilation is implemented in contributing scenarios with potential inhalation exposure. The risk characterisation ratios (RCRs) show that potential risks for worker health are controlled under the conditions of inhalation and dermal exposure. In all cases RCR ratio was < 1. Therefore it is concluded that the use of 1,3,5-trioxane in industrial and professional settings is safe for workers under the specified condition of exposure.

Short-term exposure – systemic effects

The results of experimental studies are summarized in the following table:

Table 8. Overview of experimental studies on short term toxicity (systemic effects)

Route/species	**Results**
Oral/rat	LD50: > 3200 mg/kg bw
Inhalation/rat	LC50 (4 h): > 39.2 mg/L air
Dermal/rabbit	LD50: > 3980 mg/kg bw

No acute hazard assessment is necessary for acute systemic effects as no mortality or systemic effects were observed following oral, inhalation and dermal exposure. The derivation of the respective DNEL is not required.

Short-term exposure – local effects

The results of experimental studies are summarized in the following table:

Table 9. Overview of experimental studies on short term toxicity (local effects)

Endpoint/species	Results
Skin irritation/rabbit	Not irritating
Eye irritation/rabbit	Irritating*
Skin sensitization/guinea pig	Not sensitising

* available information provides a basis for classification as an eye irritant

Currently, 1,3,5-trioxane is not classified as a skin/eye irritant or a skin sensitizer. Thus, the derivation of the respective DNEL is not required. Transient irritation of the respiratory tract irritation is the only observed acute health effect of trioxane. As there is reliable animal data available allowing the derivation of a DNEL for local inhalative effects, a quantitative exposure assessment and risk characterization is possible (DNEL=20 mg/m^3).

Long-term exposure – local and systemic effects

The results of experimental studies are summarized in the following table:

Table 10. Overview of experimental studies on short term toxicity (local and systemic effects)

Route/species	Results
Oral/rat	NOAEL: ~ 300 mg/kg/bw/d NOAEL: 200 mg/kg/bw/d
Inhalation/rat	NOAEC: 3.62 mg/l
Dermal/rabbit	waived

In a gavage study no adverse signs of toxicity were observed in rats treated in the highest tested dose level (NOAEL 300 mg/kg bw/day).
In a 2 week inhalation study with rats signs of respiratory irritation were observed in all exposure group. Though no signs of systemic toxicity were observed. Nose is the target organ for action on respiratory system.

Consumer exposure

No consumer exposure is covered by the CSAs.

Indirect exposure to humans via the environment

The conclusion of environmental exposure is that the properties of the substance give no reason for concern regarding a hazard for men via the indirect exposure route.

10. RISK CHARACTERISATION

The risk characterization of 1,3,5-trioxane has been conducted based on the DNELs in the following tables. DNELs were not derived for the general population as consumer exposure to 1,3,5-trioxane is not identified.

10.1. Exposure Scenarios

Human health

The acute toxicity of 1,3,5-trioxane is low. It is not irritant to the skin or eyes and not sensitizing to the skin. Repeated dose toxicity indicates route-specific toxicity – an oral study shows low toxicity whereas an inhalation study shows high toxicity (signs of respiratory tract irritation).
1,3,5-trioxane is not carcinogenic or mutagenic.
The reproductive study indicates developmental toxicity of 1,3,5-trioxane expressed as reduced litter size and malformation of foetal organs.
1,3,5-trioxan is listed in Annex VI, Part 3, Table 3.1 (List of harmonized classification and labelling of hazardous substances) of Regulation (EC) No 1272/2008 as reprotoxic cat. 2 (H361d: May damage the unborn child) and due to specific target organ toxicity — single exposure cat. 3 (H335: My cause respiratory irritation).
1,3,5-Trioxane is a cyclic triether (trimer of formaldehyde) which is produced from formaldehyde in the presence of an acid catalyst, in a continuous process in dedicated closed unit. The analysis of emission products generated during heating of the resin at normal operating temperatures indicated that formaldehyde was the major decomposition product. The operators working with resins based on 1,3,5-trioxane were not exposed to airborne formaldehyde high enough to cause irritant effects.

Workers

1,3,5-trioxane is produced in quantities of 100,000 - 1,000,000 t/y.
Low risk characterization ratios have been identified in all of contributing scenarios by all co-registrants demonstrating that the working conditions are fully controlled regarding exposure via inhalation and dermal routes.
The RCRs below 1 (combined routes dermal and inhalation) have been reported for all activities during manufacturing and well below 1 for use of 1,3,5-trioxane as laboratory chemical. The registrant considered relevant RPE and RMM:

- respiratory protection and chemically resistant gloves respiratory protection and specialistic full body protection
- chemically resistant gloves during operations related with use of 1,3,5-trioxane as laboratory chemical.

Consumers

There are no reported commercial or consumer uses.
Environmental Protection Agency identified a low potential that consumers might be exposed to 1,3,5-trioxane from products containing this substance. No uses in consumer products were found in data sources.

Indirect exposure of humans via the environment
The hazard classification of the substance indicates no severe toxicity with regard to possible exposure of men via the environment. The low log Kow implies that an exposure via the food is not likely. 1,3,5-trioxane is easily eliminated from water and soil via volatilization and biodegradation and therefore will not pose a risk for drinking water.
In conclusion, the toxicological and ecotoxicological properties of the substance give no reason for concern regarding a hazard for men via the indirect exposure route.

10.2 Atmospheric compartment

The test substance is not in Annex I of Regulation (EC) 2037/2000 on substances that deplete the ozone layer.
The test substance does not belong to the green house gases listed in P Foster, PV Ramaswamy et al. Changes in Atmospheric Constituents and in Radiative Forcing. In: Climate Change 2007: The Physical Basis. Contribution of Working Group I to the Fourth Assessment Report of the Intergovernmental Panel on climate Change.

10.3 Overall exposure (combined for all relevant emission /release sources)

Environment (combined for all exposure routes)

No exposure assessment was provided.
In the chemical safety assessment performed according to Article 14(3) in connection with Annex I section 3 (Environmental Hazard Assessment) and section 4 (PBT/ vPvB Assessment) no hazard was identified. Consequently all identified uses of the substance are assessed as safe for the environment.

Human health (combined for all emission sources)

All worker-related activities are assessed and all risk characterization values for long-term and short-term effects are below 1. Thus, a consideration of an overall exposure regarding worker activities is regarded to be not necessary. The risk characterization regarding the exposure of the general population towards the substance found the RCRs values for long-term and short-term exposure as well as for combined exposure below 1. Therefore it is assumed that an overall exposure does not lead to a grave risk.

Summary and conclusion

Exposure to 1,3,5-trioxane at the workplace occurs mainly via inhalation of its vapours. Analysis of available data indicates that the risk is sufficiently controlled if appropriate risk measurements measures are implemented. With respect to the identified uses reported in the registration dossiers, quantitative risk characterization was performed by comparing the inhalation and dermal exposure estimates done for each exposure scenario with the respective DNEL value.
The inhalation exposure estimate was compared to the long-term inhalation DNEL for local effects of 10 mg/m^3 and dermal exposure was compared to the long-term dermal DNEL for systemic effects of 3 mg/kg/bw/d.
1,3,5-trioxane is classified as STOT Single Exp. 3 (H335: May cause respiratory irritation). The long-term systemic DNEL should protect workers during short-term peak exposures. Therefore respiratory tract should be controlled by the use of appropriate risk management measures (i.e. personal protective equipment).
The analysis of the exposure scenarios submitted by the lead registrant as well as by the other registrants shows that in every case RCR value is well below 1 indicating that potential risks for worker health are controlled under the conditions of inhalation and dermal exposure. It is concluded that the use of trioxane presented in the CSRs is safe for workers under the specified conditions of exposure.

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