SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

Chloromethane

EC No 200-817-4

CAS No 74-87-3

Evaluating Member State(s): Italy

Dated: 26 September 2017

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Evaluating Member State Competent Authority

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Year of evaluation in CoRAP: 2012

Before concluding the substance evaluation a Decision to request further information was issued on: 1 May 2014.

Further information on registered substances here:

http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

DISCLAIMER

This document has been prepared by the evaluating Member State as a part of the substance evaluation process under the REACH Regulation (EC) No 1907/2006. The information and views set out in this document are those of the author and do not necessarily reflect the position or opinion of the European Chemicals Agency or other Member States. The Agency does not guarantee the accuracy of the information included in the document. Neither the Agency nor the evaluating Member State nor any person acting on either of their behalves may be held liable for the use which may be made of the information contained therein. Statements made or information contained in the document are without prejudice to any further regulatory work that the Agency or Member States may initiate at a later stage.

Foreword

Substance evaluation is an evaluation process under REACH Regulation (EC) No. 1907/2006. Under this process the Member States perform the evaluation and ECHA secretariat coordinates the work. The Community rolling action plan (CoRAP) of substances subject to evaluation, is updated and published annually on the ECHA web site[1].

Substance evaluation is a concern driven process, which aims to clarify whether a substance constitutes a risk to human health or the environment. Member States evaluate assigned substances in the CoRAP with the objective to clarify the potential concern and, if necessary, to request further information from the registrant(s) concerning the substance. If the evaluating Member State concludes that no further information needs to be requested, the substance evaluation is completed. If additional information is required, this is sought by the evaluating Member State. The evaluating Member State then draws conclusions on how to use the existing and obtained information for the safe use of the substance.

This Conclusion document, as required by Article 48 of the REACH Regulation, provides the final outcome of the Substance Evaluation carried out by the evaluating Member State. The document consists of two parts i.e. A) the conclusion and B) the evaluation report. In the conclusion part A, the evaluating Member State considers how the information on the substance can be used for the purposes of regulatory risk management such as identification of substances of very high concern (SVHC), restriction and/or classification and labelling. In the evaluation report part B the document provides explanation how the evaluating Member State assessed and drew the conclusions from the information available.

With this Conclusion document the substance evaluation process is finished and the Commission, the Registrant(s) of the substance and the Competent Authorities of the other Member States are informed of the considerations of the evaluating Member State. In case the evaluating Member State proposes further regulatory risk management measures, this document shall not be considered initiating those other measures or processes. Further analyses may need to be performed which may change the proposed regulatory measures in this document. Since this document only reflects the views of the evaluating Member State, it does not preclude other Member States or the European Commission from initiating regulatory risk management measures which they deem appropriate.

[1] http://echa.europa.eu/regulations/reach/evaluation/substance-evaluation/community-rolling-action-plan

Contents

Part A. Conclusion

1. CONCERN(S) SUBJECT TO EVALUATION

Chloromethane was originally selected for substance evaluation in order to clarify concerns about:

- Human health/CMR;
- Suspected Endocrine Disruptor
- Risk characterisation ratio close to 1 (human health)

During the evaluation also other concerns were identified. The additional concerns were:

- environmental exposure assessment and risk characterisation

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

None.

3. CONCLUSION OF SUBSTANCE EVALUATION

The evaluation of the available information on the substance has led the eMSCA to the following conclusions, as summarised in the table below.

Table 1

CONCLUSION OF SUBSTANCE EVALUATION Conclusions	Tick box
Need for follow-up regulatory action at EU level	X
Harmonised Classification and Labelling	X
Identification as SVHC (authorisation)	
Restrictions	
Other EU-wide measures	
No need for regulatory follow-up action at EU level	

4. FOLLOW-UP AT EU LEVEL

On the basis of the available information, an harmonized classification of the substance is envisaged by eMSCA, as a follow-up at EU level by adding the following hazard category: mutagenicity and toxicity for reproduction.

5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

5.1. No need for regulatory follow-up at EU level

6. TENTATIVE PLAN FOR FOLLOW-UP ACTIONS (IF NECESSARY)

The eMSCA has the intention to prepare an Annex XV dossier with a proposal for harmonized classification and labelling. The intention will be included in the RoI tentatively by the first half of 2018.

Part B. Substance evaluation

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

Chloromethane was originally selected for substance evaluation in order to clarify concerns about:

- Human health/CMR;
- Suspected Endocrine Disruptor;
- Risk characterisation ratio close to 1 (human health).

During the evaluation also other concerns were identified. The additional concerns were:

- Environmental exposure assessment and risk characterisation.

The Substance evaluation started on March 2012.

The concern with carcinogenicity is confirmed. However, no further information is requested or follow-up at EU level envisaged since two carcinogenicity studies in rats and mice are available and the substance has already an harmonised classification as carcinogenicity category 2, H351 (Suspected of causing cancer).

During the substance evaluation process eMSCA confirmed the suspected concern for mutagenicity and suggested a revision of the harmonised classification process for this end point.

The concern for reproductive toxicity raised during the manual screening has been confirmed during the 12-month evaluation and lead to a request in the SEv decision. This request has been addressed by the Registrant(s). The new submitted data on developmental toxicity showed no developmental effects of chloromethane, while the clear-cut evidence of testicular toxicity in the rat, which is especially evident at concentrations above 1000 mg/m³ supports the classification of chloromethane in category 2 for effects on fertility. A revision of the harmonised classification process for this end point should be performed.

Regarding endocrine disruptor proprierties, in a reproductive toxicity test (Chapin et al. 1984): "The authors' had proposed that chloromethane acts centrally to lower circulating testosterone." In the updated dossier the Registrant(s) provided detailed information demonstrating that the substance is not an "endocrine disruptor" as defined by WHO/IPCS (2002).

Concerning the human exposure, in the updated dossier Risk Management Measures (RMMs) - such as Local Exhaust Ventilation and Personal Protective Equipments (gloves) - are proposed to adequately control the risk. Therefore, the revised RCR values showed an adequate control of the risks.

During the evaluation an additional concern with environmental exposure assessment and risk characterisation was identified. Missing elements to clarify this concern were requested by a SEv decision. This concern is now clarified by the new information provided by the Registrants.

Table 2

EVALUATED ENDPOINTS	
Endpoint evaluated	**Outcome/conclusion**
Endpoint 1 Carcinogenicity	Carcinogenicity is confirmed. No further information is requested as the substance has already an harmonised classification as carc. 2.
Endpoint 2 Mutagenicity	The mutagenicity was confirmed and an harmonised classification process is envisaged since neither an harmonised nor a self-classification is available for this endpoint.
Endpoint 3 Toxicity for Reproduction/Developmental toxicity	The potential concern on developmental toxicity was not confirmed by the new submitted study (PNDT 2nd species). eMSCA supports the classification of chloromethane in Cat. 2 for effects on fertility, therefore a revision of the harmonized classification for this end point should be performed.
Endpoint 4 Suspected Endocrine Disruptor	In the updated dossier the registrant provided detailed information demonstrating that the substance is not an "endocrine disruptor" as defined by WHO/IPCS (2002). No further action requested.
Endpoint 5 Risk characterisation ratio close to 1 (human health)	Risk management measures (RMMs), such as Local Exhaust Ventilation and Personal Protective Equipments (gloves) are proposed to adequately control the risk. No further action requested.
Endpoint 6 Environmental exposure assessment and risk characterisation	Requests fulfilled by the registrants. No further action is needed

7.2. Procedure

The Substance evaluation of the Chloromethane has started on March 2012.
The initial grounds for concern relating to: human health/CMR; Suspected Endocrine Disruptor; Risk characterisation ratio close to 1 (human health).
In the course of the evaluation, the evaluating MSCA noted additional concern regarding environmental exposure assessment and risk characterisation with potential human risk via the environment.
The evaluating MSCA considered that further information was required to clarify the above mentioned concerns. Therefore, it prepared a draft decision pursuant to Article 46(1) of the REACH Regulation to request further information. It submitted the draft decision to ECHA on 28 February 2013.
After discussion in the Member State Committee meeting on 3-7 February 2014, a unanimous agreement of the Member State Committee on the draft decision as modified at the meeting was reached on 5 February 2014. ECHA took the decision on 1 May 2014 pursuant to Article 51(6) of the REACH Regulation.
eMSCA had interactions with the Registrant and following that interactions, the Registrant have made dossier updates and eMSCA took into account the updated dossier.

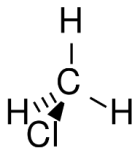
7.3. Identity of the substance

Table 3

SUBSTANCE IDENTITY	
Public name:	Chloromethane
EC number:	200-817-4
CAS number:	74-87-3
Index number in Annex VI of the CLP Regulation:	602-001-00-7
Molecular formula:	CH3Cl
Molecular weight range:	--
Synonyms:	Methane Chloride, Methyl Chloride

Type of substance ☒ Mono-constituent ☐ Multi-constituent ☐ UVCB

Structural formula:



7.4. Physico-chemical properties

Table 4

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES	
Property	**Value**
Physical state at 20°C and 101.3 kPa	At room temperature chloromethane is a colourless gas
Vapour pressure	5 732.9 hPa at 25àC
Water solubility	5320 mg/L at 25°C
Partition coefficient n-octanol/water (Log Kow)	log Pow: 0.91
Flammability	Extremely flammable, lower & upper explosion limits 7.1 & 18.5 %, respectively
Explosive properties	study technically not feasible
Oxidising properties	--
Granulometry	--
Stability in organic solvents and identity of relevant degradation products	--
Dissociation constant	--

7.5. Manufacture and uses

7.5.1. Quantities

Table 5

AGGREGATED TONNAGE (PER YEAR)				
☐ 1 – 10 t	☐ 10 – 100 t	☐ 100 – 1000 t	☐ 1000- 10,000 t	☐ 10,000-50,000 t
☐ 50,000 – 100,000 t	☐ 100,000 – 500,000 t	☐ 500,000 – 1000,000 t	☒ > 1000,000 t	☐ Confidential

7.5.2. Overview of uses

This substance is manufactured and/or imported in the European Economic Area in 1 000 000 - 10 000 000 tonnes per year.
This substance is used in the following products: laboratory chemicals, washing & cleaning products and extraction agents. This substance has an industrial use resulting in manufacture of another substance (use of intermediates).
This substance is used in the following areas: formulation of mixtures and/or re-packaging and scientific research and development. This substance is used for the manufacture of: chemicals and rubber products.
Release to the environment of this substance is likely to occur from industrial use: as an intermediate step in further manufacturing of another substance (use of intermediates), manufacturing of the substance and in processing aids at industrial sites. Other release to the environment of this substance is likely to occur from: indoor use as reactive substance.

Table 6

USES	Use(s)
Uses as intermediate	--
Formulation	Manufacture
Uses at industrial sites	Use as intermediate in industrial manufacture of chemicals Use as industrial solvent
Uses by professional workers	Use as laboratory agent
Consumer Uses	--
Article service life	--

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

The substance is currently listed on Annex VI of CLP Regulation ((EC) No 1272/2008).

Table 7

HARMONISED CLASSIFICATION ACCORDING TO ANNEX VI OF CLP REGULATION (REGULATION (EC) 1272/2008)							
Index No	**International Chemical Identification**	**EC No**	**CAS No**	**Classification**		**Spec. Conc. Limits, M-factors**	**Notes**
				Hazard Class and Category Code(s)	**Hazard statement code(s)**		
602-001-00-7	chloromethane methyl chloride	200-817-4	74-87-3	Press. Gas Flamm. Gas 1 Carc. 2 STOT RE 2*	 H220 H351 H373**		Note U

7.6.2. Self-classification

- In the registration(s):

Press. Gas (Liq)	H280
Repr. 2	H361 (Inhalation)

- The following hazard classes are in addition notified among the aggregated self-classifications in the C&L Inventory*:*

Skin Corr. 1A	H314
Skin Corr. 1B	H314
Acute Tox. 2	H330
Acute Tox. 3	H331
Acute Tox. 4	H332

7.7. Environmental fate properties

Hydrolysis of chloromethane is not expected to play an important role in the abiotic degradation since it is relatively slow within normal pH regimes in the aquatic environments. Atmospheric half-life is estimated to be approximately one year. Chloromethane is readily biodegradable and available information suggests that does not bioaccumulate.

7.7.1. Degradation

Concerning abiotic degradation, hydrolysis of chloromethane in water is relatively slow with a half-life ranging from 62 days to about 1.1 year at 25 °C and pH 7 (Mabey and Mill, 1978). At pH 11, hydrolysis takes place at a slow rate, yielding methanol as a transformation product (ICCA HPV-SIDS, 2004).

Regarding phototrasformation in air, the experimental half-life is 360 d (Atkinson, 1989) and the calculated half-life according to SRC AOPWIN is 310 d. The exact pathway for decomposition in the troposphere is not known; however, the ultimate degradation products would be HCl, CO and CO2 (Spence et al., 1976; Singh et al., 1982). The direct

photolysis of chloromethane appears unimportant in the troposphere (Shold and Rebbert, 1978).

Concerning biotic degradation, the Registrant(s) included in the updated dossier a new reliable ready biodegradation study, conducted according to a standard test protocol (OECD Guideline 301D, Ready biodegradability Closed Bottle test) and in compliance with GLP. Chloromethane was biodegraded by 77% at day 28, meeting the ten day window.

The Registrant(s) concluded that the substance is readily biodegradable and based on the available information, the eMSCA can support this conclusion.

Concerning water and sediment simulation tests the Registrant(s) proposed a data waiving. In accordance with Column 2 of REACH Annex IX, the simulation test on ultimate degradation in surface water and the sediment simulation test (required in Sections 9.2.1.2 and 9.2.1.4 respectively) do not need to be conducted as the substance is readily biodegradable, the eMSCA can support this conclusion.

The Registrant(s) proposed a data waiving also for the soil simulation test. In accordance with Column 2 of REACH Annex IX, the full soil simulation test does not need to be conducted as the substance is readily biodegradable, the eMSCA can support this conclusion.

7.7.2. Environmental distribution

The adsorption coefficient Koc has been calculated to be 13.22 (SRC KOCWIN v2.00). Due to the low value of Koc the adsorption to soil and sediment is expected to be low.
With respect to the aqueos compartment the Henry's Law constant H at 24 °C is 894 Pa m3/mol (Gossett, 1987). Due to the high value of H the substance will tend to evaporate from the water surface to the atmosphere.

For the determination of environmental distribution of the registered substance the Registrant(s) proposed a Mackay Level III simulation. Emission of chloromethane directly to air resulted in >99% of the total chemical mass residing in the air compartment, with advection in air representing the primary mechanism of removal. Degradation in air represented only a minor amount of the total chemical mass (< 1%) removed from the system. Intermedia exchange of chloromethane between the other compartments was insignificant. Similar results were obtained when the chloromethane emission was to the soil compartment. Because of the relatively high vapour pressure of chloromethane, only 3.6% of the total chemical mass remained in the soil compartment whereas 96% was found in the air compartment. Hence, the primary removal process from soil was volatilization and the primary removal process from the system was advection in air. Local persistence was about 4 days, regardless if the chloromethane emission was to the air or soil compartment. In contrast to that observed for emission to the air and soil compartments, emission of chloromethane to the water compartment resulted in only about 20% the total chemical mass residing in the air, whereas about 80% remained in the water. Intermedia exchange of chloromethane with the other compartments (e.g., soil and sediment) was insignificant. Advection and degradation in water removed significant amounts (28% and 2.4%, respectively) of the total chemical mass. Nonetheless, local persistence was about 15 days. The above results indicate that the environmental compartments of concern, based on emission of chloromethane, are air and water. Insignificant amounts of chloromethane are expected to be found in the soil or sediment compartments, regardless of source of entry to the environment. Since chloromethane is a gas, most industrial releases are expected to be directly to the air compartment.

7.7.3. Bioaccumulation

The measured octanol/water partition coefficient (log Kow of 0.91) is low, indicating a low potential for bioaccumulation and low tendency of adsorption to soil and sediment.

Concerning bioaccumulation the Registrant(s) proposed a data waiving. In accordance with Column 2 of REACH Annex IX, the study on aquatic bioaccumulation (required in Section 9.3.2) does not need to be conducted as the substance has a low potential for bioaccumulation, the eMSCA can support this conclusion.
The calculated bioconcentration factor for chloromethane, based on a log Kow of 0.91 is 3.16 (SRC EPISUITE v4.00).

The Registrant(s) concluded the substance is not bioaccumulative and based on the available information, the eMSCA can support this conclusion.

7.8. Environmental hazard assessment

7.8.1. Aquatic compartment (including sediment)

7.8.1.1. Fish

Chloromethane is a volatile substance and the test system should consider precautions to maintain costant the test concentrations. The available experimental acute toxicity studies on fish were not carried out in a closed system, therefore the results, based on nominal concentration, could underestimate the substance effects. The acute toxicity of chloromethane was estimated using a QSAR model (ECOSAR), based on the related chemical group of the Narcosis Class I type compounds. The predicted result was a 96h LC50 of 396 mg/L, that was considered reliable for the purpose of CSA.

The Registrants waived information on the effects on long-term toxicity on fish on the base of the toxicological profile of chloromethane on aquatic organisms and on the base of exposure considerations, in accordance with Column 2 of REACH Annex IX.
Based on the available information, the eMSCA can support this conclusion.

7.8.1.2. Aquatic invertebrates

A reliable study on Daphnia magna was conducted under static-renewal test conditions (renewel at 24h) in a closed (no headspace) system and analysis of exposure solutions following 24 hours of aging in closed vessels without headspace showed little to no loss of test substance. The test followed the OECD 202 guide line and showed a 48h EC50 of 200 mg/L, based on nominal concentrations. The result was comparable to the available QSAR model (ECOSAR) predictions on aquatic invertebrates, based on the related chemical group of the Narcosis Class I type compounds. The lowest acute toxicity value was obtained from the experimental study on Daphnia magna and was considered reliable for the purpose of CSA.

The Registrants waived information on the effects on long-term toxicity on invertebrates on the base of the toxicological profile of chloromethane on aquatic organisms and on the base of exposure considerations, in accordance with Column 2 of REACH Annex IX.
Based on the available information, the eMSCA can support this conclusion.

7.8.1.3. Algae and aquatic plants

Experimental toxicity studies on algae were available, however it was unclear from the description of the tests if they were carried out in a closed system. Therefore the results, based on nominal concentration, could underestimate the substance effects. The toxicity of chloromethane was estimated using a QSAR model (ECOSAR), based on the related chemical group of the Narcosis Class I type compounds. The predicted result was a 96h LC50 of 231 mg/L, based on growth rate, that was considered reliable for the purpose of CSA.

Based on the available information, the eMSCA can support this conclusion.

7.8.1.4. Sediment organisms

The Registrant(s) provide a justification for sediment organisms toxicity waiving:
"In Annex X of the Regulation (EC) No 1907/2006 REACH concerning the Registration, Evaluation, Authorisation of Chemicals (REACH), it is suggested, that "long-term toxicity testing shall be proposed by the registrant if the results of the chemical safety assessment indicates the need to investigate further the effects of the substance and/or relevant degradation products on sediment organisms. The choice of the appropriate test(s) depends on the results of the chemical safety assessment. "

The Registrants based their waiving justification on the fact that chloromethane is a gas and has a low potential for adsorption (log Koc = 1.12) and bioaccumulation (log Kow = 0.91). Therefore exposure of sediment organisms is unlikely and testing towards sediment dwelling organisms not necessary. Furthermore, the equilibrium partitioning method can be used for assessing the hazard of sediment organisms.

The eMSCA can support this conclusion.

7.8.2. Terrestrial compartment

The Registrant(s) provide a justification for terrestrial organisms toxicity waiving:
"In accordance with column 2 of REACH AnnexIX, the study must not be conducted if exposure to soil and sediment is unlikely".

The Registrants based their waiving justification on the fact that chloromethane is gaseous and the primary environmental compartment to which it partition is air. In accordance with REACH regulation, the studies need not to be conducted if exposure to soil and sediment is unlikely. Volatilization of chloromethane from moist soil surfaces is expected to be an important fate process. Considering its solubility, volatility and resultant Henry's Law Constant, chloromethane is expected, under equilibrium conditions, to exist principally in the air. Mackay Level III simulations were used to evaluate the effect of source of entry on the distribution and persistence of chloromethane. As expected the emission of chloromethane directly to air resulted in > 99% of the total chemical mass residing in the air compartment. Only insignificant amounts of chloromethane will be found in the soil or sediment compartments, regardless of source of entry to the environment. Since chloromethane is a gas, most industrial releases are expected to be directly to the air compartment.

In conclusion the substance is readily biodegradable, has a low potential for adsorption (log Koc = 1.12) and does not bioaccumulate (log Kow = 0.91). These characterists suggest a small hazardous potential towards soil organisms. Therefore, the equilibrium partitioning method has been used to assess the hazard potential of chloromethane for soil organisms.

The eMSCA can support this conclusion.

7.8.3. Microbiological activity in sewage treatment systems

One study is available for bacteria, the reported TTC (24 h) value was 500 mg/L for Pseudomonas putida but it is unclear from the description of the available studies if vessels were closed or not. Because all results are based on nominal concentrations, a reliability score of 3 is assigned (not reliable). Results on methanogenic bacteria (Blum et al, 1991a and 1991b) were EC50 values of 39 mg/L after 24h and 50 mg/L after 48 h, but the results are inconsistent and the documentation is insufficient for assessment. Additionally a Nitrobacter test (Tang, 1992) shows a IC50 of 2010 mg/L after 24 h (inhibition of NO2-N production). Because all results are based on nominal concentration all test results should be evaluated with caution because optimum test conditions (i.e. measured concentrations, closed system) were not met.

Most chloromethane that finds its way into a bio-oxidation wastewater treatment system is likely to volatilize directly to the air. Based on the fugacity model STPWIN® (USEPA 2000), 77% of the chloromethane that enters the model treatment facility is volatilized directly to the air and 22% released with the final effluent (SIDS, 2002).

7.8.4. PNEC derivation and other hazard conclusions

Table 8

PNEC DERIVATION AND OTHER HAZARD CONCLUSIONS		
Hazard assessment conclusion for the environment compartment	**Hazard conclusion**	**Remarks/Justification**
Freshwater	PNEC (freshwater): 0.2 mg/L	Assessment factor: 1000 One short-term experimental result on invertebrate and QSAR estimates on the acute toxicity from the three trophic levels were available. All the results were comparable and the lowest EC50 value was 200 mg/L, obtained from the study on Daphnia magna. Therefore, according to ECHA guidance, an assessment factor of 1000 can be applied to the lowest short-term result.
Marine water	PNEC (marine waters): 0.02 mg/L	Assessment factor: 10000 Aquatic toxicity data were available only on freshwater organisms. According to ECHA guidance, an assessment factor of 10000 can be applied to the lowest short-term result from freshwater toxicity studies. Therefore the EC50 of 200 mg/L, obtained from the study on Daphnia magna, was used to derive the PNEC marine waters.
Intermittent releases to water	PNEC (intermittent releases): 2 mg/L	Assessment factor: 100 According to ECHA guidance, an assessment factor of 100 can be applied to the lowest short-term result. The lowest result was a EC50 of 200 mg/L obtained from a study on Daphnia magna, and was used to derive the PNEC intermittent releases.
Sediments (freshwater)	PNEC sediment (freshwater): 0.98 mg/kg sediment dw	Extrapolation method: partition coefficient

		Considering its solubility, volatility and resultant Henry's Law Constant, chloromethane is expected, under equilibrium conditions, to exist principally in the air. Additionally, the substance is not expected to adsorb to suspended solids and sediment based upon the log Koc. To complete the data, the PNEC sediment is derived from the partition coefficient method.
Sediments (marine water)	PNEC sediment (marine water): 0.098 mg/kg sediment dw	Extrapolation method: partition coefficient Considering its solubility, volatility and resultant Henry's Law Constant, chloromethane is expected, under equilibrium conditions, to exist principally in the air. Additionally, the substance is not expected to adsorb to suspended solids and sediment based upon the log Koc. To complete the data, the PNEC sediment (marine) is derived from the partition coefficient method.
Sewage treatment plant	PNEC STP: 0.3 mg/l	Assessment factor: 10 Extrapolation method: Assessment factor PNEC STP is derived from OECD 301D test concentration at wich toxicity to the inoculum can be ruled out and an assessment factor of 10.
Soil	PNEC soil: 0.14 mg/kg soil dw	Extrapolation method: partition coefficient Considering its solubility, volatility and resultant Henry's Law Constant, chloromethane is expected, under equilibrium conditions, to exist principally in the air. Additionally, the substance is not expected to adsorb to suspended solids and sediment based upon the log Koc. To complete the data, the PNEC soil is derived from the partition coefficient method.

7.8.5. Conclusions for classification and labelling

On the basis of the available information, the substance is not classified for environment according to Regulation EC No 1272/2008.

7.9. Human Health hazard assessment

7.9.1. Toxicokinetics

The toxicokinetics, metabolism and distribution pattern of chloromethane was thoroughly summarized in peer reviewed documents.

Inhalation is the only likely route of exposure of humans to chloromethane. Most inhaled chloromethane is metabolized and excreted. As part of the detoxification process chloromethane is readily conjugated to glutathione and may be excreted in the urine, the metabolites being undistinguishable from other metabolites. In addition, some chloromethane may be metabolized and excreted as one-carbon fragments.

eMSCA supports the Registrants' conclusion.

7.9.2. Acute toxicity and Corrosion/Irritation

Not evaluated.

7.9.3. Sensitisation

Not evaluated.

7.9.4. Repeated dose toxicity

Not evaluated.

7.9.5. Mutagenicity

Under normal conditions chloromethane exists as a gas. Therefore, the only relevant route of exposure is via inhalation. The tests reported below were mostly conducted in exposure chambers.
The following in vitro and in vivo studies were conducted with chloromethane:

In bacterial reverse mutation assays with Salmonella typhimurium (Ames tests), chloromethane was shown to induce gene mutations in the test strains detecting base pair substitutions , namely TA 100 (Simmon et al.1977, NTP, 1991) and TA 1535 (Andrews et al., 1976) with and without metabolic activation system. In contrast, no mutation induction was observed using TA 98 (NTP, 1991) and TA 1537 both in the presence and absence of metabolic activation. Moreover, a concentration-related increase in the 8-azaguanine-resistent fraction in S. typhimurium TM 677 was observed (Fostel et al., 1985).

Using a mammalian gene mutation assay in established TK6 human lymphoblasts, Fostel et al. (1985) detected a dose-related increase in the mutant frequency after exposure to 0-5% of chloromethane. In addition, Fostel et al. (1985) demonstrated that chloromethane exposure caused a statistically significant concentration-related induction of sister chromatid exchanges (SCE) frequency in the same cell line; chloromethane caused also a significant decline in the mitotic index and inhibited cell-cycle kinetics. Unscheduled DNA synthesis (UDS) could be detected in spermatocyte and hepatocyte primary cell cultures after exposure to 1-10% chloromethane, but not in tracheal epithelial cells (Working et al., 1986)

No induction of UDS was evident in spermatocytes, hepatocytes, or tracheal epithelial cells from rats exposed to concentrations of 6195-7228 mg/m³ for 6 h/day for 5 days (Working et al., 1986), while acute exposure to a concentration close to the maximum tolerated dose (30975 mg/m³, 3 h), caused a marginal increase in UDS in hepatocytes, but not in spermatocytes and tracheal epithelial cells (Working et al., 1986). Thus, these data suggest that chloromethane appears to be a weak, direct-acting genotoxicant. While activity could be measured in hepatocytes and spermatocytes directly in vitro, only high concentrations of chloromethane elicited a response in the whole animal, and then only in hepatocytes.

Jäger et al. (1988) and Ristau et al. (1989 et 1990) performed alkaline elution assays in mice.

Jäger et al. (1988) found no elevation in formaldehyde concentrations in livers and kidneys ex vivo after a single exposure of mice of both sexes to 1000 ppm methyl chloride. Moreover, no DNA-protein crosslinks and only minor evidence of single-strand breaks were found in the kidneys of male mice after exposure to 1000 ppm methyl chloride during 4 days, for 6 h / day.

On the other hand Ristau et al. (1989) detected DNA-protein crosslinks (DPC) in the renal tissue of male mice exposed to 1000 ppm of methyl choride for 8 hours and sacrificed immediately after exposure (as opposed to 5-6 hrs post-exposure period in the Jager et al. 1988 study) to minimize repair of DNA lesions. These authors conducted a subsequent time-course study of renal DNA lesions in male B6C3F1 mice exposed for 8 hr to 1000 ppm of methyl chloride and sacrificed at 0, 5, or 48 hr post-exposure, or exposed 6 hr/day for 4 days and sacrificed 0 or 5 hr post-exposure (Ristau et al., 1990). In the single-exposure groups, evidence for DPC, but not single strand breaks (SSB), was again observed immediately after exposure; at 5 hr postexposure, DPC were no longer apparent, but there was evidence of SSB; by 48 hr, no significant indications of either DPC or SSB were found. In the 4-day exposure groups, only a slight indication of DPC at 0 hr post-exposure and low levels of SSB 5 hr later were reported. These data indicate that chloromethane induces DPC that are rapidly repaired. The observed SSB can be attributed to the excision repair of DPC and/or to the formation of free-radicals resulting from methyl chloride-induced GSH depletion and associated lipid peroxidation.

The rapid kinetic of DPC repair could explain the negative results reported by Jäger et al. 1988 after a 5-6 hours post-exposure period. Ristau el al. propose that DPC may result from formaldehyde formed during methyl chloride exposure, and that DNA lesions could contribute to the renal tumorigenicity of methyl chloride observed only in male mice.

In a dominant lethal assays, dose independent increases of pre- and post-implantation losses were detected after chloromethane exposure (Working et al., 1985, Chellman et al., 1986). However the authors conclude that "dominant lethal effects of MeCl are probable consequences of its induction of epididymal inflammation, rather than a direct effect of MeCl or its proposed metabolites", as demonstrated by parallel experiments in which the concomitant treatment with the anti-inflammatory agent BW755C totally abolishes the effects (Chellman et al., 1986).

In macromolecular binding studies with 14C -chloromethane radio-labelled carbon could be detected in lipid, RNA, DNA, and protein from isolated liver, kidneys, lungs, and testes of male rats, but methylation was not evident (Kornbrust et al., 1982, Peter et al. 1985). However, the detected incorporation of 14C into these macromolecules was most likely due to its metabolism via the one carbon pool, in particular through the formation of formaldehyde. Nevertheless the possibility that chloromethane might, to a lesser extent, bind directly to macromolecules cannot be excluded (Löf, A. et al. ;2000).

In conclusion the available studies demonstrate that chloromethane is clearly genotoxic *in vitro*, both in bacteria and in mammalian cells. *In vivo*, methyl chloride was demonstrated to form DNA-protein cross-link in the renal tissue (that is also the target for carcinogenicity) and to induce UDS in rat hepatocytes, although only at exposure levels close to the MTD. A direct genotoxic effect in germ cells is considered unlikely, however the testicle

inflammation reported in the lethal dominat study suggests that the substance is able to reach the gonadal tissue and in consideration of the genotoxic properties of the substance a genotoxic effect cannot be excluded.

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

In vitro:
Bacterial reverse mutation assay: positive
Mammalian cell gene mutation assay (Fostel *et al*., 1985): positive
Sister chromatid exchange assay in mammalian cells (Fostel *et al*., 1985): positive
UDS in rats hepatocytes, spermatocytes (Working *et al*. 1986): positive.

In vivo:
Unscheduled DNA synthesis (Working *et al*. 1986): negative at low doses (6195-7228 mg/m³ for 6 h/day for 5 days) and positive in acute dose (to a concentration close to the maximum tolerated dose: 30975 mg/m³, 3 h).
DNA binding study (Peter *et al*. 1985): negative
DNA-protein cross link (alkaline elution assay; Jäger *et al*. 1988): DPC negative after exposure to 1000 ppm chloromethane during 4 days, for 6 h / day in mice liver and kidney ex vivo.
DNA-protein cross link (alkaline elution assay; Ristau *et al*., 1989): DPC positive in the kidney ex vivo of male mice after a single exposure of 8 hrs to 1000 ppm chloromethane.
Repair of DNA-protein crosslinks (Ristau *et al*. 1990): positive for DNA single strand breaks as effect of DNA repair system of DPC.

Dominant lethal assay (Chellman et al. 1986; Working et al. 1985): positive for pre-implantation and post-implantation losses, likely due to the secondary effect of local inflammation.

Value used for CSA: Genetic toxicity: positive.

Justification for classification or non classification
Chloromethane is clearly genotoxic *in vitro*. DNA protein cross-links were detected *in vivo* in the kidney (target organ for carcinogenicity) of treated mice. Positive in UDS in rat hepatocytes at acute dose close to the maximum tolerated dose. A revision of the harmonized classification and labelling for this hazard class should be performed.

7.9.6. Carcinogenicity

Chloromethane has been classified in Carcinogenicity Category 2 H351 (Suspected of causing cancer).according to C&L of the GHS based on the presence of renal neoplastic leasions were detected in male mice. Based on the available information, the eMSCA supports the conclusion on this endpoint.

No further information are needed to be required to clarify the concern for carcinogenicity.

7.9.7. Toxicity to reproduction (effects on fertility and developmental toxicity)

Effects on fertility
A two-generation reproduction study on rats (inhalation exposure) showed a clear-cut and dose-related reduction of male fertility, with a concurrent increase of testicular pathology. Effects on testes and fertility were observed at 475 mg/m³ with a NOAEC of 150 mg/m³; therefore the LOAEC and NOAEC for male reproductive toxicity in the two-generation study were comparable and lower, respectively than the NOAEC for systemic effects (465 mg/m³) derived from the 2-year inhalation study for rats. Overall the data indicate a susceptibility of the male reproductive system to chloromethane exposure.
Further investigation indicated that the testicular damage induced by short-term exposure may be reversible; no data exist on the potential reversibility after prolonged exposure.

Supportive evidence on the testicular toxicity of Chloromethane was provided by
- two old 2-year inhalation studies in mice and rats where testicular lesions were also observed after exposure to chloromethane at 1000 mg/m³.
- a dominant lethal study in the rat showing an increase of pre-implantation losses at the tested concentrations of 1000 and 3000 mg/m³. Testicular histology was examined at the highest exposure level, showing a marked alteration of spermiation and epidyimal inflammation.
Overall, the findings on Chloromethane-induced male reproductive toxicity do not indicate that genotoxic or endocrine-related mechanisms are primarily involved. The testicular effects of Chloromethane can be convincingly attributed to a direct cytotoxic effect on the spermatogenic cycle.
In conclusion, the clear-cut evidence of testicular toxicity in the rat, which is especially evident at concentrations above 1000 mg/m³ supports the classification of chloromethane in category 2 for effects on fertility in line with the self-classification provided by the REGs. Therefore, a revision of the harmonized classification and labelling for this hazard class should be performed.

Developmental toxicity
The eMSCA considered the original database with rats and mice not sufficient for the evaluation of developmental toxicity and requested an OECD 414 study in non-rodents (rabbits) to clarify this suspected concern with chloromethane.
Indeed the available developmental studies in rodents showed that chloromethane, upon exposure during organogenesis, induced heart defects in mice also at exposure without a concurrent maternal toxicity. No such effect, nor other developmental effects, was seen in rats. In addition, teratogen mode of action was not clear and the initial findings n mice were only partly replicated by further studies in the same species. Therefore a developmental toxicity study on rabbits (OECD 414) has been requested in order to assess the susceptibility related to the species and clarify the concern with this endpoint.
The registrant carried out the study in 2015. The study showed that exposure of rabbits to 0, 250, 500 or 1000 ppm did not induce any developmental toxicity.
The eMSCA agrees with the conclusion of the study. Therefore it is concluded that the potential developmental toxicity observed in mice is likely related to a species-specific effect. Based on the available evidence, chloromethane needs not to be classified as a developmental toxicant.

7.9.8. Hazard assessment of physico-chemical properties

None impacting human health.
The substance is currently listed on Annex VI of CLP Regulation ((EC) No 1272/2008) in particular concerning the physico-chemical properties the substance in classified as Flam. Gas 1 (H220).

7.9.9. Selection of the critical DNEL(s)/DMEL(s) and/or qualitative/semi-quantitative descriptors for critical health effects

Table 9

CRITICAL DNELS/DMELS					
Endpoint of concern	**Type of effect**	**Critical study(ies)**	**Corrected dose descriptor(s) (e.g. NOAEL, NOAEC)**	**DNEL/ DMEL**	**Justification/ Remarks**
Inhalation Workers repeated dose toxicity	Systemic effects - Long-term	two-generation toxicity study in rats	$NOAEC_{corr}$ of 156 mg/m³	12.5 mg/m³	**AF for other interspecies differences:** 2.5 (Default AF) **AF for intraspecies differences:** 5 (Default AF for workers) **Overall Assessment Factor:** 12.5

7.9.10. Conclusions of the human health hazard assessment and related classification and labelling

On the basis of the available information, an harmonized classification of the substance is envisaged by eMSCA, as a follow-up at EU level by adding the following hazard category: mutagenicity and toxicity for reproduction.

7.10. Assessment of endocrine disrupting (ED) properties

7.10.1. Endocrine disruption – Environment

Not evaluated.

7.10.2. Endocrine disruption - Human health

In the previous dossier no information was provided by the Registrant on the possible endocrine-related effects. The initial concern was related to the fact that adrenal lesions and lower testosterone levels were observed in toxicological studies on rodents (Chellman *et al*. 1986a; Morgan et al. 1982).

For this reason the eMSCA requested the Registrant to address this concern. In the updated dossier the registrant provided detailed information demonstrating that the substance is not an "endocrine disruptor" as defined by WHO/IPCS (2002). Indeed the effects of chloromethane on sperm quality and fertility are due to a direct toxicity on the testes (see section 7.9.7 for conclusion on classification on fertitlity) and not mediated by adverse changes in hormone concentrations. The eMSCA agrees with this conclusion.

7.11. PBT and VPVB assessment

Persistence

Based on the results of the ready biodegradality study, the Registrant(s) concluded that the substance is not expected to be persistent in the environment and it does not meet the P or vP criteria. The eMSCA can support this conclusion.

Bioaccumulation

Due to the low log Kow value, the Registrant(s) concluded the substance does not meet the B o vB criteria. The eMSCA can support this conclusion.

Toxicity

Chloromethane is classified as STOT RE category 2. Thus, chloromethane meets the toxicity criteria (T) based on mammalian effects.

Overall conclusion

Taking into account the available information, although the substance fulfils the criteria for toxicity, the data indicate that chloromethane is neither fulfilling the criteria for persistence and bioaccumulation. Therefore, the eMSCA can support the Registrant conclusion that the substance is not PBT/vPvB.

7.12. Exposure assessment

7.12.1. Human health

7.12.1.1. Worker

For all the identified uses exposure scenarios have been developed and a quantitative estimation of the exposure levels has been carried out. Since chloromethane is a gas and is handled under high industrial standard, exposure via the dermal route is limited. Thus, no exposure calculation for the dermal route is performed.

The exposure levels have been estimated by using the ECETOC TRA worker v 3.1.
Risk management measures (RMMs), such as Local Exhaust Ventilation and Personal Protective Equipments (gloves) are proposed to adequately control the risk.

7.12.1.2. Consumer

Not relevant: chloromethane is not used by consumers.

7.12.2. Environment

The Registrant(s) state that "due to the exclusive use of chloromethane in industrial and professional settings, no exposure calculation and risk characterization for the general population is necessary" and that "since chloromethane is a gas and is handled under high industrial standard".
Moreover, the Registrant(s) state that "Chloromethane is only used in industrial and professional settings, but not by consumers. The described exposure scenarios cover the manufacture, use as an intermediate in chemical processes, and use as industrial solvent" and that "The assessment of all industrial uses is based on generic scenarios. Critical release rates, covering all site specific conditions, were determined in a scaling approach. The exposure calculation follows a worst case. For each scenario the highest annual use

was combined with the highest identified release rates. Default values were applied where applicable".
The eMSCA agrees on the Registrant's approach: while ERC defaults are used for release fractions to air and soil, the release fractions to sewage for industrial uses were derived based on the approved critical release rate and the annual tonnage, taking into account the release times per year.
In the generic approach chosen by the Registrant, a critical release rate to sewage water was determined by iterative calculation of exposure estimates. The critical release rate corresponds to the highest release rate where all environmental RCRs demonstrate safe use (i.e., taking into account a safety margin, that they are still below 0.9).
The eMSCA supports the Registrant's recommendations regarding the release fraction to sewage.

7.12.2.1. Aquatic compartment (incl. sediment)

In the CSR, the Registrant(s) provide PECs for local freshwater, freshwater sediment, marine water and marine water sediment and the regional PECs in surface water (total), sediment (total), sea water (total) and sea water sediment (total).

The eMSCA agrees on the generic approach chosen by the Registrant(s) to calculate the PECs, using the ERC for release fractions to air and soil, and the release fractions to sewage for industrial uses were derived based on the approved critical release rate and the annual tonnage.

7.12.2.2. Terrestrial compartment

In the CSR, the Registrant(s) provide PEC for local soil and regional PECs in agricultural soil, natural soil (total) and industrial soil (total).

The eMSCA agrees on the generic approach chosen by the Registrant(s) to calculate the PECs, using the ERC for release fractions to air and soil, and the release fractions to sewage for industrial uses were derived based on the approved critical release rate and the annual tonnage.

7.12.2.3. Atmospheric compartment

In all exposure scenarios of CSR, for the local release fractions to air default values by the corresponding ERCs are applied.

The eMSCA agrees on the generic approach chosen by the Registrant(s) to calculate the PECs, using the ERC for release fractions to air and soil, and the release fractions to sewage for industrial uses were derived based on the approved critical release rate and the annual tonnage.

7.12.3. Combined exposure assessment

As stated in the CSR by the Registrant(s), Chloromethane enters the environment from natural and industrial sources, but natural sources of chloromethane dominate by far over anthropogenic sources (...). The industrial amount of chloromethane introduced into the environment must be seen in the context of the background input due to natural sources and the available data on aquatic organisms show toxicities of chloromethane far in excess

of natural occurring concentrations. The combined exposure assessment was calculated by the Registrant(s) taking into account all emission source and the regional release.

7.13. Risk characterisation

Human Health

Workers

For all the relevant scenarios identified safe uses are demonstrated.

Due to the substance characteristics as well as the exposure conditions, DNEL for long-term systemic effects via inhalation route has been derived only.

According to RCR calculated, no unacceptable risk can occur during the manufacture and distribution of the substance, when the specified RMM are followed. Risk management measures (RMMs), such as Local Exhaust Ventilation and Personal Protective Equipments (gloves) are proposed to adequately control the risk.

Environment

Chloromethane enters the environment from natural and industrial sources. The eMSCA agrees on the Registrant's argumentation.

Aquatic compartment (incl. sediment)

The reported RCRs are less than 1

Terrestrial compartment

The reported RCRs are less than 1

Atmospheric compartment

Microbiological activity in sewage treatment systems

The reported RCRs are less than 1

Overall risk characterization

Environment (combined for all exposure routes)

The Registrant(s) provide the regional release estimations and the corresponding RCRs are less than 1. Moreover, the calculated regional releases from all uses are reported.

7.14. References

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7.15. Abbreviations

AF Assessment factor
BW Body weight
CAS Chemical abstracts service
C&L Classification and labelling
CLP Classification, labelling and packaging (Regulation (EC) No 1272/2008)
CMR Carcinogenicity, mutagenicity and toxicity to reproduction
CSR Chemical Safety Report
DMEL Derived Minimal Effect Level
DNEL Derived no effect level
ES Exposure Scenario
eMSCA Evaluating Member State Competent Authority
NOAEC No Observed Adverse Effect Concentration
NOAEL No Observed Adverse Effect Level
NOEC No Observed Effect Concentration
OECD Organisation for Economic Co-operation and Development
PBT Persistent, Bioaccumulative, Toxic
PEC Predicted Environmental Concentration
PNEC Predicted No Effect Concentration
RCR Risk characterization ratio
RMMs Risk Management Measures
vPvB Very Persistent and very Bioaccumulative