CHEMICAL SAFETY REPORT

Substance name: bis(2-methoxyethyl) ether (diglyme)

EC number: 203-924-4

CAS number: 111-96-6

Applicant's identity: ISOCHEM

Authorisation application: Use of diglyme as a process solvent in one step of the manufacturing of an Active Pharmaceutical Ingredient used in an anti-protozoal drug.

PUBLIC VERSION

9. EXPOSURE ASSESSMENT (and related risk characterisation)

9.0. Introduction

9.0.1. Overview of uses and Exposure Scenarios

Diglyme (CAS Nr. 111-96-6) is used as a process solvent in the manufacturing of an intermediate for an active pharmaceutical ingredient (API), called P2, at the applicant production site. P2 is toll-manufactured for a pharmaceutical company, which uses it as an active ingredient in an anti-protozoal drug.

At the applicant site 4 to 6 batches of P2 are produced per year. Each batch lasts ca. 2 weeks for the manufacturing of the intermediate P1; 4 to 5 weeks for the whole synthesis process P0 + P1 + P2, see below). Every batch is equivalent to the use of 5'600 kg of diglyme. Per year between 22'400 kg and 33'600 kg of diglyme is used. Diglyme is supplied in 200 kg drums by a manufacturer in the EU. The annual fresh solvent use is limited to ca. 500 kg, as diglyme is recycled on site by distillation to be re-used in the process.

Diglyme is an aprotic, polar solvent with a boiling point of 162°C. Diglyme is chemically compatible with the main reagents used in the manufacturing of P2, which are: the precursor P0, sodium borohydride (NaBH4), Lewis acid, chloroform and hydrogen chloride. Diglyme is a flammable liquid that may release explosive vapours. For this reason, strict safety measures apply during handling and use.

The manufacturing of P2 is a complex process that consists of three steps:

- The first step is the manufacturing of a precursor P0 and does not use diglyme.
- The second step is the manufacturing of P1. In this step diglyme is used as a process solvent.
- The third step is the manufacturing of P2, which does not use diglyme.

In the manufacturing step involving diglyme, the carboxylic acid group in P0 is reduced to an alcohol in the presence of sodium borohydride, lewis acid, and diglyme as process solvent. Two reactors are used in this process: diglyme is pumped under exhaust ventilation from a 200 kg drum via a dip pipe with attached flexi-hose, which is placed into the drum, into the reactor (R10) containing the precursor P0. In another reactor (R13), diglyme is mixed with sodium borohydride. Subsequently, Lewis acid gas is introduced into reactor R10. From reactor R13, the NaBH4/diglyme mixture is slowly pumped via a balloon into reactor R10, containing the precursor P0/diglyme mixture. The reactors are equipped with scrubbers to collect possible air emissions. After addition of water to the reaction mixture, the diglyme/water/product mixture is pumped into reactor R13, where ammonia is added to increase the pH. The mixture is extracted with chloroform: the water phase containing traces of diglyme is separated from the mixture and transferred to a waste storage tank followed by incineration on site. The organic phase (chloroform + diglyme + product) is transferred through a filter to tank R22 and then pumped into reactor R13 where HCl gas is introduced which converts the product into a salt P1 (which is a solid). Chloroform is removed by distillation. Subsequently, the product is collected on a filter and mother liquids (containing diglyme + CHCl3 + HCl) are transferred to an agitated tank containing water + sodium hydroxide. The product on the filter is rinsed several times with chloroform. The chloroform is sent to the agitated tanks with mother liquids. The product P1, which contains traces of chloroform and diglyme) is unloaded from the filter and stored in a bag. From the agitated tank, the organic phase (chloroform and diglyme) is pumped into reactor R13, where chloroform is distilled off into a storage tank. The remaining diglyme (+ traces of chloroform) is pumped into reactor R12, where diglyme is distilled off under vacuum and stored into 200 kg drums. Remaining residues of the distillation are transferred to the waste tank to be incinerated on site. The reactors and agitated tanks are cleaned with water or methanol using a spray ball. Methanol is distilled off and put back into the reactor to clean the distillation circuit. After cleaning, the waste is transferred to the appropriate waste tank.

In step 3 of the manufacturing process, P1 is converted into P2. This step does not involve the use of diglyme.

At the site, 5 teams of 8 workers are involved in the production of P2, which means potentially 40 workers could be in contact with diglyme. The manufacturing process is a batch process in a closed system, with no significant opportunity for exposure of workers or release to the environment. PROC 1, PROC 3 and PROC 4 have been used to assess the exposure of workers to diglyme during more generic tasks, like monitoring

equipment or conducting tasks for other stages of the process with do not involve potential direct contact with diglyme. The exposure estimates are related to a full 8-hour shift as operators will be present in the manufacturing building the whole day.

For other tasks, where more opportunities for exposure of workers to diglyme arise, the following PROCs are used:

1. PROC 8b: for the transfer of diglyme from a 200 kg drum to the reactor and transfer of solvent waste (containing a low percentage of diglyme) from the reactor to waste storage tanks
2. PROC 9: for sampling of a small volume of the reaction solution for the purpose of process and quality control, and transfer to the laboratory in a small container
3. PROC 15: for quality control and analytical processing by laboratory staff
4. PROC 8a: for maintenance and cleaning operations

Transfer of diglyme:

From drums to reactor:
The operator fixes a flexible ventilation hose connected to a scrubber on the drum. The operator is equipped with a gas mask (carbon cartridge ABEK2HGP3 with a screw-on filter DIN 148 in aluminum housing: this protects against inorganic and organic gases and vapours with a boiling point > 65 °C), and nitrile gloves (EN374). The operator opens the drum and introduces a pipe into the drum connected to the reactor through a pump. At the end, the operator closes the empty drum and repeats the same operation with another drum. The average duration for the whole transfer of diglyme from the drums to the reactor is 1 hour.

From reactor to reactor:
Flexible pipes and pump are those that have been used to load diglyme from the drums to the reactors. The transfer line is closed. At the end of the transfer from reactor R13 containing diglyme + NaBH4 to reactor R10, the transfer line is rinsed with water from R13 to R10 to eliminate diglyme.

For the other transfers, the process is the same. Pump, flexible and rigid pipes are dedicated to the reactor during the production process and are cleaned with the reactor during the cleaning step.

Sampling:
The operator is equipped with a gas mask (carbon cartridge ABEK2HGP3 with a screw-on filter DIN 148 in aluminium housing: this protects against inorganic and organic gases and vapours with a boiling point > 65 °C), and nitrile gloves (EN374). The operator fixes a flexible ventilation hose connected to a scrubber close to the sampling valve. The operator opens the valve and pours the product to be analysed into a sampling bottle. The operator closes the sampling valve and closes the sampling bottle. The operation duration is less than 2 minutes.

Quality control:
The technician wears safety goggles and nitrile gloves (EN374). The technician opens the bottle in a fume cupboard and prepares the sample for the analysis. The sample is injected in the analysis device (GC, HPLC or KF). All waste are collected in closed containers and finally sent to the waste tank before incineration. The average duration of the sample preparation is 5 minutes.

Maintenance and cleaning:
Cleaning procedure is done in closed conditions. The operator introduces the appropriate solvent (water or methanol) in the closed reactor. The reactor is equipped with a spray ball. The cleaning solvent is pumped from the bottom of the reactor through a pump to the spray ball in a loop and in closed conditions. All equipment (pump, flexible and rigid pipe) are decontaminated as such. The distillation line of the reactor is cleaned by methanol reflux. At the end, the cleaning solvent is sent through dedicated pipes to the waste tank before incineration.

All maintenance operations are done after complete decontamination of the equipment.

T**onnage information:**

Assessed tonnage: 35.0 tonnes/year based on:

- 35.0 tonnes/year used

The following table list all the exposure scenarios (ES) assessed in this CSR.

Table 5. Overview of exposure scenarios and contributing scenarios

Identifiers	Market Sector	Titles of exposure scenarios and the related contributing scenarios	Tonnage (tonnes per year)
ES1 - IW1		Use at industrial site - Use at industrial site as process solvent - Industrial use of processing aids in processes and products, not becoming part of articles (ERC 4) - Use in closed process, no likelihood of exposure (PROC 1) - Use in closed batch process (synthesis or formulation) (PROC 3) - Use in batch and other process (synthesis) where opportunity for exposure arises (PROC 4) - Maintenance and cleaning operations (PROC 8a) - Transfer of diglyme - charging of the reactor (PROC 8b) - Sampling and transport to the laboratory (PROC 9) - Use as laboratory reagent (PROC 15)	35.0
Manufacture: M-#, Formulation: F-#, Industrial end use at site: IW-#, Professional end use: PW-#, Consumer end use: C-#, Service life (by workers in industrial site): SL-IW-#, Service life (by professional workers): SL-PW-#, Service life (by consumers): SL-C-#.)			

9.0.2. Introduction to the assessment

9.0.2.1. Environment

Scope and type of assessment

The exposure scenarios in the current CSR are tailored to supporting the application for authorisation of bis(2-methoxyethyl)ether (diglyme) for its use as solvent in the manufacture of an active pharmaceutical ingredient (API). The solvent diglyme does not end up in the final API. However, the solvent use in the manufacturing process is subject to authorisation under REACH, requiring the assessment of human and environmental exposure and their potentially associated risks.

According to Regulation (EC) No 1907/2006, Article 62(4)(d), an environmental risk assessment would not be required in this CSR for an authorisation application, as only the risks arising from the intrinsic properties specified in Annex XIV need to be considered. However, in order to be complete, the exposure estimates and the associated risks for the environment have been included in this CSR.

The human health risks related to the classification of diglyme as a reproductive toxicant are assessed in the current CSR, with only the dermal and inhalation route being relevant for risks arising from occupational exposure. Health hazards for the general population, however, may potentially also arise due to exposure via the environment (vapour, via the food chain). However, in view of the risk management measures in place at the applicant's production facility (collection of all solvent waste, and disposal by incineration), emissions of diglyme to the aquatic environment are effectively prevented. Emissions to air cannot be completely excluded in view of the low airborne residues that may be generated during the phases of handling of diglyme. However, since diglyme is strictly processed in closed systems the only opportunity for release to ambient air and consequently to the environment is identified at charging of diglyme into the closed system.

The scope of exposure assessment and type of risk characterisation required for the environment are described in the following table, based on the hazard conclusions presented in section 7 of the CSR submitted by the lead registrant for diglyme.

Table 6. Type of risk characterisation required for the environment

Protection target	Type of risk characterisation	Hazard conclusion (see section 7)
Freshwater	Quantitative	PNEC aqua (freshwater) = 6.4 mg/L
Sediment (freshwater)	Quantitative	PNEC sediment (freshwater) = 27.4 mg/kg sediment dw
Marine water	Quantitative	PNEC aqua (marine water) = 0.64 mg/L
Sediment (marine water)	Quantitative	PNEC sediment (marine water) = 2.74 mg/kg sediment dw
Sewage treatment plant	Quantitative	PNEC STP = 50 mg/L
Air	Not needed	No hazard identified
Agricultural soil	Quantitative	PNEC soil = 1.72 mg/kg soil dw
Predator	Quantitative	PNEC oral = 2.77 mg/kg food

Comments on assessment approach:

The regional concentrations are reported in section 10.2.1.2 (see Table 16, "Predicted regional exposure concentrations (Regional PEC)"). The local Predicted Exposure Concentrations (PECs) reported for each contributing scenario correspond to the sum of the local concentrations (Clocal) and the regional concentrations (PEC regional).

Caution: The exposure estimates have been obtained with EUSES although the following parameter(s) is/are outside the boundaries of the EUSES model:

- Water solubility (940 g/L)

Although - following Regulation (EC) No 1907/2006, Article 62(4)(d) - the CSR supporting an application for authorisation needs to cover only those risks arising from the intrinsic properties specified in Annex XIV, the environmental exposure and the associated risks have been included in the CSR.

9.0.2.2. Man via environment

Scope and type of assessment

The scope of exposure assessment and type of risk characterisation required for man via the environment are described in the following table based on the hazard conclusions reported and justified in section 5.11.

Table 7. Type of risk characterisation required for man via the environment

Route of exposure and type of effects	Type of risk characterisation	Hazard conclusion (see section 5.11)
Inhalation: Systemic, long-term	Quantitative	DNEL (Derived No Effect Level) = 0.3 mg/m³
Oral: Systemic, long-term	Quantitative	DNEL (Derived No Effect Level) = 0.09 mg/kg bw/day

Comments on assessment approach:

Humans may potentially be exposed to diglyme via the environment. Since strict emission control measures are implemented, limiting releases to the aquatic environment (and to soil) to zero, the only relevant exposure path is inhalation of vapours emitted from the facility to air.

Emissions to air are estimated based on worst-case assumptions: the release factor is adopted from the TGD (2003), Appendix I, Table A1.1 (release factor 0.0001). The number of release days is specified following the applicant's specification of the production process (4 to 6 campaigns per year).

9.0.2.3. Workers

Scope and type of assessment

The scope of exposure assessment and type of risk characterisation required for workers are described in the following table based on the hazard conclusions presented in section 5.11.

Table 8. Type of risk characterisation required for workers

Route	Type of effect	Type of risk characterisation	Hazard conclusion (see section 5.11)
Inhalation	Systemic, long-term	Quantitative	DNEL (Derived No Effect Level) = 1.68 mg/m³
	Systemic, acute	Not needed	No hazard identified
	Local, long-term	Not needed	No hazard identified
	Local, acute	Not needed	No hazard identified
Dermal	Systemic, long-term	Quantitative	DNEL (Derived No Effect Level) = 0.24 mg/kg bw/day
	Systemic, acute	Not needed	No hazard identified
	Local, long-term	Not needed	No hazard identified
	Local, acute	Not needed	No hazard identified
Eye	Local	Not needed	No hazard identified

Comments on assessment approach related to toxicological hazard:

Diglyme was included into Annex XIV of the REACH Regulation (the list of substances subject to authorisation) due to its intrinsic properties as being toxic to reproduction (classification as Repr 1B, H360FD – may damage fertility; may damage the unborn child.).

Following Regulation (EC) No 1907/2006, Article 62(4)(d), the CSR supporting an application for authorisation needs to cover only those risks arising from the intrinsic properties specified in Annex XIV. The health effects resulting from the intrinsic hazardous properties of diglyme are:
- Effects (impairment) on male reproductive organs
- Developmental toxicity: increased incidence of resorption and a higher risk of malformations

The DNELs used in this CSR were derived by ECHA'S Risk Assessment Committee (RAC). Based on the dose-response relationship, developmental toxicity was identified as the most critical effect. Therefore, the DNELs are considered to be sufficiently protective against the critical effects and also against any other health effects, if relevant. Estimates of inhalation and dermal exposure were calculated using the ECETOC TRA 3.0 model.

Comments on assessment approach related to physicochemical hazard:

Not relevant.

General information on risk management related to toxicological hazard:

Exposure of workers handling diglyme in the course of the manufacturing process is restricted to the lowest possible level: there is no open handling of diglyme at any stage of the process.

A brief summary of the risk management measures related to the toxicological hazard is given as follows:

Diglyme charging from drums into the reactors is performed under exhaust ventilation. PPE of operators consists of chemical protective suit (Nomex®), air respirator (carbon cartridge ABEK2HGP3 with a screw-on filter DIN 148 in aluminium housing; this protects against inorganic and organic gases and vapours with a boiling point > 65 °C), and solvent resistant protective nitrile rubber gloves (EN374).

Operators are trained to the use of PPE when working with CMR products. A specific SOP (Standard Operating Procedure) describes how to manipulate CMR products. This procedure is reviewed by EHS department on regular basis. All operators are asked to respect this SOP and to sign the familiarization form at each review. According to this SOP, a dedicated area is materialized around the charging point (roughly 2 meters around) to prevent presence of unequipped people. These operations are conducted in a ventilated workshop (enhanced

general ventilation 5 air changes per hour)

Use of diglyme in the manufacturing process occurs in a completely closed reactors that are connected to other equipment by hard piping; therefore, there is no possibility of exposure under normal process conditions. Filtration of the finished precipitate is performed automatically using an enclosed suction filter that does not require manual intervention. Solvent waste (containing diglyme) is discharged to the waste tank via hard piping. PPE for operators consists of chemical protective suits (Nomex®), solvent-resistant gloves (EN374) and boots.

Sampling for quality control from the reactor is conducted using an integrated process sampler that allows tight attachment of the sample jar and is enclosed in a sealable box. The operator fixes a flexible ventilation hose connected to a scrubber close to the sampling valve. The operator opens the valve and pours the product to be analysed into a sampling bottle. The operator closes the sampling valve and closes the sampling bottle. PPE of operators consists of chemical protective suit (Nomex®), air respirator (carbon cartridge ABEK2HGP3 screw-on filter DIN 148 in aluminum housing; this protects against inorganic and organic gases and vapours with a boiling point >65 °C), and solvent resistant protective nitrile rubber gloves (EN374).

During cleaning of reactors and other equipment, operators are wearing a chemical protective suit (Nomex®), an air respirator (carbon cartridge ABEK2HGP3 with a screw-on filter DIN 148 in aluminum housing), solvent-resistant nitrile rubber gloves (EN374) and boots.

All activities for quality control (analysis by HPLC) are performed in a fume cupboard, the volumes handled are very small. PPE consists of safety goggles and solvent-resistant protective gloves (EN374).

Solvent waste is transferred to a waste storage tank and incinerated on site.

General information on risk management related to physicochemical hazard:

Not relevant.

9.0.2.4. Consumers

Exposure assessment is not applicable as there are no consumer-related uses for the substance.

9.1. Exposure scenario 1: Use at industrial site - Use at industrial site as process solvent

Sector of use:
SU 9, Manufacture of fine chemicals

Environment contributing scenario(s):	
Industrial use of processing aids in processes and products, not becoming part of articles	ERC 4
Worker contributing scenario(s):	
Transfer of diglyme - charging of the reactor	PROC 8b
Use in closed process, no likelihood of exposure	PROC 1
Use in closed batch process (synthesis or formulation)	PROC 3
Use in batch and other process (synthesis) where opportunity for exposure arises	PROC 4
Maintenance and cleaning operations	PROC 8a
Sampling and transport to the laboratory	PROC 9
Use as laboratory reagent	PROC 15

Explanation on the approach taken for the ES

9.1.1. Environmental contributing scenario 1: Industrial use of processing aids in processes and products, not becoming part of articles

9.1.1.1. Conditions of use

Amount used, frequency and duration of use (or from service life)
• Daily use at site: <= 0.5 tonnes/day
• Annual use at a site: <= 35 tonnes/year
• Percentage of EU tonnage used at regional scale: = 100 %
Conditions and measures related to sewage treatment plant
• Municipal STP: No [Effectiveness Water: 0%]
Conditions and measures related to treatment of waste (including article waste)
• Particular considerations on the waste treatment operations: No (low risk) (ERC based assessment demonstrating control of risk with default conditions. Low risk assumed for waste life stage. Waste disposal according to national/local legislation is sufficient.)
Other conditions affecting environmental exposure
• Discharge rate of effluent: >= 2E3 m3/d
• Receiving surface water flow rate: >= 1.8E4 m3/d

9.1.1.2. Releases

The local releases to the environment are reported in the following table.

Table 9. Local releases to the environment

Release	Release factor estimation method	Explanation / Justification
Water	Release factor	**Initial release factor:** 0% **Final release factor:** 0% **Local release rate:** 0 kg/day **Explanation / Justification:** Diglyme used is recycled and re-used in the process. Any liquid waste containing traces of diglyme is submitted to a solvent waste storage tank via fixed piping, and then incinerated on site. Release to wastewater is strictly avoided.

Release	Release factor estimation method	Explanation / Justification
Air	Release factor	**Initial release factor:** 0.01% **Final release factor:** 0.01% **Local release rate:** 0.05 kg/day **Explanation / Justification:** The amount of diglyme emitted via exhaust air is estimated to be 0.01%, based on the release factors given in the TGD (2003). Diglyme has a boiling point of 162°C and a vapour pressure of 60 Pa at 20°C. The release factor is 0.0001.
Soil	Release factor	**Final release factor:** 0% **Explanation / Justification:** There is no release to soil as the manufacturing process is completely closed, diglyme is recycled and re-used in the process and any liquid waste containing traces of diglyme is collected in a waste storage tank and incinerated on site.

Releases to waste

Release factor to waste from the process: 0%

Diglyme is recycled and re-used in the process. Liquid waste containing traces of diglyme is collected in a waste storage tank and is incinerated on site.

Release factor to waste from on-site treatment: 0%

All waste on the applicant site is collected in waste storage tanks and is further processed by distillation and incineration. 80% of the waste is incinerated on site, 20% is refined externally (but not diglyme).

9.1.1.3. Exposure and risks for the environment and man via the environment

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 10. Exposure concentrations and risks for the environment

Protection target	Exposure concentration	Risk characterisation
Freshwater	**Local PEC:** 1.598E-8 mg/L	RCR < 0.01
Sediment (freshwater)	**Local PEC:** 6.839E-8 mg/kg dw	RCR < 0.01
Marine water	**Local PEC:** 1.616E-9 mg/L	RCR < 0.01
Sediment (marine water)	**Local PEC:** 6.915E-9 mg/kg dw	RCR < 0.01
Predator (freshwater)	**Local PEC:** 2.257E-8 mg/kg ww	RCR < 0.01
Predator (marine water)	**Local PEC:** 2.282E-9 mg/kg ww	RCR < 0.01
Top predator (marine water)	**Local PEC:** 2.282E-9 mg/kg ww	RCR < 0.01
Sewage treatment plant	**Local PEC:** 0 mg/L	RCR < 0.01
Agricultural soil	**Local PEC:** 1.295E-6 mg/kg dw	RCR < 0.01
Predator (terrestrial)	**Local PEC:** 1.912E-6 mg/kg ww	RCR < 0.01
Man via environment - Inhalation	**Local PEC:** 2.666E-6 mg/m³	RCR < 0.01
Man via environment - Oral	**Exposure via food consumption:** 1.809E-5 mg/kg bw/day	RCR < 0.01
Man via environment - combined routes		RCR < 0.01

Table 11. Contribution to oral intake for man via the environment from local contribution

Type of food	Estimated daily dose	Concentration in food
Drinking water	1.374E-7 mg/kg bw/day	4.808E-6 mg/L
Fish	3.708E-11 mg/kg bw/day	2.257E-8 mg/kg ww
Leaf crops	1.792E-5 mg/kg bw/day	0.001 mg/kg ww
Root crops	2.466E-8 mg/kg bw/day	4.496E-6 mg/kg ww
Meat	2.434E-10 mg/kg bw/day	5.661E-8 mg/kg ww
Milk	4.536E-9 mg/kg bw/day	5.661E-7 mg/kg ww

Conclusion on risk characterisation

The results of the risk assessment show that the RCRs for all environmental compartments are clearly below 1.

9.1.2. Worker contributing scenario 1: Transfer of diglyme - charging of the reactor (PROC 8b)

9.1.2.1. Conditions of use

Diglyme charging has been described in detail in section 9.0.1. Operators are wearing an air respirator and nitrile gloves (EN374) while charging the reactors with diglyme and other reagents. The average duration for the whole transfer of diglyme from the drums to the reactor is ca. one hour.

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Workers 3.0
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Workers 3.0
Technical and organisational conditions and measures	
• General ventilation: Enhanced general ventilation (5-10 air changes per hour)	TRA Workers 3.0
• Containment: Semi-closed process with occasional controlled exposure	TRA Workers 3.0
• Local exhaust ventilation: yes [Effectiveness Inhal: 95%]	TRA Workers 3.0
• Local exhaust ventilation (for dermal): yes [Effectiveness Dermal: 95%]	TRA Workers 3.0
• Occupational Health and Safety Management System: Advanced	TRA Workers 3.0
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95%]	TRA Workers 3.0
• Respiratory Protection: Yes (Respirator with APF of 10) [Effectiveness Inhal: 90%]	TRA Workers 3.0
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Workers 3.0
• Process temperature (for liquid): <= 40 °C	TRA Workers 3.0
• Skin surface potentially exposed: Two hands (960 cm2)	TRA Workers 3.0

9.1.2.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 12. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.042 mg/m³** (TRA Workers 3.0)	RCR = 0.025
Dermal, systemic, long-term	**0.034 mg/kg bw/day** (TRA Workers 3.0)	RCR = 0.143
Combined routes, systemic, long-term		RCR = 0.168

Conclusion on risk characterisation

The RCRs for long-term, systemic exposure to the substance via the inhalation and dermal route, as well as via the combined routes, are clearly below 1.

9.1.3. Worker contributing scenario 2: Use in closed process, no likelihood of exposure (PROC 1)

9.1.3.1. Conditions of use

Use of diglyme in the manufacturing process occurs in a completely closed reactors that are connected to other equipment by hard piping; therefore, there is no possibility of exposure under normal process conditions.

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Workers 3.0
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Workers 3.0
Technical and organisational conditions and measures	
• General ventilation: Enhanced general ventilation (5-10 air changes per hour)	TRA Workers 3.0
• Containment: Closed system (minimal contact during routine operations)	TRA Workers 3.0
• Local exhaust ventilation: no [Effectiveness Inhal: 0%]	TRA Workers 3.0
• Occupational Health and Safety Management System: Advanced	TRA Workers 3.0
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: No [Effectiveness Dermal: 0%]	TRA Workers 3.0
• Respiratory Protection: No [Effectiveness Inhal: 0%]	TRA Workers 3.0
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Workers 3.0
• Process temperature (for liquid): <= 40 °C	TRA Workers 3.0
• Skin surface potentially exposed: One hand face only (240 cm2)	TRA Workers 3.0

9.1.3.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 13. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.017 mg/m³** (TRA Workers 3.0)	RCR < 0.01
Dermal, systemic, long-term	**0.034 mg/kg bw/day** (TRA Workers 3.0)	RCR = 0.142
Combined routes, systemic, long-term		RCR = 0.152

Conclusion on risk characterisation

The RCRs for long-term, systemic exposure to the substance via the inhalation and dermal route, as well as via the combined routes, are clearly below 1.

9.1.4. Worker contributing scenario 3: Use in closed batch process (synthesis or formulation) (PROC 3)

9.1.4.1. Conditions of use

Use of diglyme in the manufacturing process occurs in a completely closed reactors that are connected to other equipment by hard piping; therefore, there is no possibility of exposure under normal process conditions.

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Workers 3.0
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Workers 3.0
Technical and organisational conditions and measures	
• General ventilation: Enhanced general ventilation (5-10 air changes per hour)	TRA Workers 3.0
• Containment: Closed batch process with occasional controlled exposure	TRA Workers 3.0
• Local exhaust ventilation: yes [Effectiveness Inhal: 90%]	TRA Workers 3.0
• Local exhaust ventilation (for dermal): no [Effectiveness Dermal: 0%]	TRA Workers 3.0
• Occupational Health and Safety Management System: Advanced	TRA Workers 3.0
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95%]	TRA Workers 3.0
• Respiratory Protection: No [Effectiveness Inhal: 0%]	TRA Workers 3.0
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Workers 3.0
• Process temperature (for liquid): <= 40 °C	TRA Workers 3.0
• Skin surface potentially exposed: One hand face only (240 cm2)	TRA Workers 3.0

9.1.4.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 14. Exposure concentrations and risks for workers

Route of exposure and type of effects	**Exposure concentration**	**Risk characterisation**
Inhalation, systemic, long-term	**0.503 mg/m³** (TRA Workers 3.0)	RCR = 0.299
Dermal, systemic, long-term	**0.035 mg/kg bw/day** (TRA Workers 3.0)	RCR = 0.144
Combined routes, systemic, long-term		RCR = 0.443

Conclusion on risk characterisation

The RCRs for long-term, systemic exposure to the substance via the inhalation and dermal route, as well as via the combined routes, are clearly below 1.

9.1.5. Worker contributing scenario 4: Use in batch and other process (synthesis) where opportunity for exposure arises (PROC 4)

9.1.5.1. Conditions of use

Use of diglyme in the manufacturing process occurs in a completely closed reactors that are connected to other equipment by hard piping; therefore, there is no possibility of exposure under normal process conditions.

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Workers 3.0
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 8 hours	TRA Workers 3.0
Technical and organisational conditions and measures	
• General ventilation: Enhanced general ventilation (5-10 air changes per hour)	TRA Workers 3.0
• Containment: Semi-closed process with occasional controlled exposure	TRA Workers 3.0
• Local exhaust ventilation: yes [Effectiveness Inhal: 90%]	TRA Workers 3.0
• Local exhaust ventilation (for dermal): yes [Effectiveness Dermal: 90%]	TRA Workers 3.0
• Occupational Health and Safety Management System: Advanced	TRA Workers 3.0
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95%]	TRA Workers 3.0
• Respiratory Protection: No [Effectiveness Inhal: 0%]	TRA Workers 3.0
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Workers 3.0
• Process temperature (for liquid): <= 40 °C	TRA Workers 3.0
• Skin surface potentially exposed: Two hands face (480 cm2)	TRA Workers 3.0

9.1.5.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 15. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.839 mg/m³** (TRA Workers 3.0)	RCR = 0.499
Dermal, systemic, long-term	**0.034 mg/kg bw/day** (TRA Workers 3.0)	RCR = 0.143
Combined routes, systemic, long-term		RCR = 0.642

Conclusion on risk characterisation

The RCRs for long-term, systemic exposure to the substance via the inhalation and dermal route, as well as via the combined routes, are clearly below 1.

9.1.6. Worker contributing scenario 5: Maintenance and cleaning operations (PROC 8a)

9.1.6.1. Conditions of use

During cleaning of reactors and other equipment, operators are wearing a chemical protective suit, an air respirator, solvent-resistant nitrile rubber gloves (EN374) and boots. All maintenance operations are operated after complete decontamination of the equipment.

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Workers 3.0
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 4 hours	TRA Workers 3.0
Technical and organisational conditions and measures	
• General ventilation: Enhanced general ventilation (5-10 air changes per hour)	TRA Workers 3.0
• Containment: No	TRA Workers 3.0
• Local exhaust ventilation: yes [Effectiveness Inhal: 90%]	TRA Workers 3.0
• Local exhaust ventilation (for dermal): yes [Effectiveness Dermal: 90%]	TRA Workers 3.0
• Occupational Health and Safety Management System: Advanced	TRA Workers 3.0
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95%]	TRA Workers 3.0
• Respiratory Protection: No [Effectiveness Inhal: 0%]	TRA Workers 3.0
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Workers 3.0
• Process temperature (for liquid): <= 40 °C	TRA Workers 3.0
• Skin surface potentially exposed: Two hands (960 cm2)	TRA Workers 3.0

9.1.6.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 16. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**1.006 mg/m³** (TRA Workers 3.0)	RCR = 0.599
Dermal, systemic, long-term	**0.069 mg/kg bw/day** (TRA Workers 3.0)	RCR = 0.286
Combined routes, systemic, long-term		RCR = 0.885

Conclusion on risk characterisation

The RCRs for long-term, systemic exposure to the substance via the inhalation and dermal route, as well as via the combined routes, are below 1.

9.1.7. Worker contributing scenario 6: Sampling and transport to the laboratory (PROC 9)

9.1.7.1. Conditions of use

When sampling from the reactor, the operator fixes a flexible ventilation hose connected to a scrubber close to the sampling valve. The operator opens the valve and pours the product to be analysed into a sampling bottle. The operator closes the sampling valve and closes the sampling bottle. The operation duration is usually less than 2 minutes. For the exposure and risk assessment with the TRA tool, a duration of < 1 hour is used.

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Workers 3.0
Amount used (or contained in articles), frequency and duration of use/exposure	

	Method
• Duration of activity: < 1 hour	TRA Workers 3.0
Technical and organisational conditions and measures	
• General ventilation: Enhanced general ventilation (5-10 air changes per hour)	TRA Workers 3.0
• Containment: Semi-closed process with occasional controlled exposure	TRA Workers 3.0
• Local exhaust ventilation: yes [Effectiveness Inhal: 90%]	TRA Workers 3.0
• Local exhaust ventilation (for dermal): yes [Effectiveness Dermal: 90%]	TRA Workers 3.0
• Occupational Health and Safety Management System: Advanced	TRA Workers 3.0
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95%]	TRA Workers 3.0
• Respiratory Protection: No [Effectiveness Inhal: 0%]	TRA Workers 3.0
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Workers 3.0
• Process temperature (for liquid): <= 40 °C	TRA Workers 3.0
• Skin surface potentially exposed: Two hands face (480 cm2)	TRA Workers 3.0

9.1.7.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 17. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.168 mg/m³** (TRA Workers 3.0)	RCR = 0.1
Dermal, systemic, long-term	**0.034 mg/kg bw/day** (TRA Workers 3.0)	RCR = 0.143
Combined routes, systemic, long-term		RCR = 0.243

Conclusion on risk characterisation

The RCRs for long-term, systemic exposure to the substance via the inhalation and dermal route, as well as via the combined routes, are clearly below 1.

9.1.8. Worker contributing scenario 7: Use as laboratory reagent (PROC 15)

9.1.8.1. Conditions of use

All activities for quality control (analysis by HPLC) are performed in a fume cupboard, the volumes handled are very small. PPE consists of safety goggles and solvent-resistant protective gloves (EN374). The average duration of the sample preparation is usually less than 5 minutes. For the exposure and risk assessment with the TRA tool, a duration of < 1 hour is used.

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Workers 3.0
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 1 hour	TRA Workers 3.0
Technical and organisational conditions and measures	
• General ventilation: Enhanced general ventilation (5-10 air changes per hour)	TRA Workers 3.0
• Containment: No	TRA Workers 3.0

	Method
• Local exhaust ventilation: yes [Effectiveness Inhal: 90%]	TRA Workers 3.0
• Local exhaust ventilation (for dermal): no [Effectiveness Dermal: 0%]	TRA Workers 3.0
• Occupational Health and Safety Management System: Advanced	TRA Workers 3.0
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (chemically resistant gloves conforming to EN374 with specific activity training) [Effectiveness Dermal: 95%]	TRA Workers 3.0
• Respiratory Protection: No [Effectiveness Inhal: 0%]	TRA Workers 3.0
Other conditions affecting workers exposure	
• Place of use: Indoor	TRA Workers 3.0
• Process temperature (for liquid): <= 40 °C	TRA Workers 3.0
• Skin surface potentially exposed: One hand face only (240 cm2)	TRA Workers 3.0

9.1.8.2. Exposure and risks for workers

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 18. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.168 mg/m³** (TRA Workers 3.0)	RCR = 0.1
Dermal, systemic, long-term	**0.017 mg/kg bw/day** (TRA Workers 3.0)	RCR = 0.071
Combined routes, systemic, long-term		RCR = 0.171

Conclusion on risk characterisation

The RCRs for long-term, systemic exposure to the substance via the inhalation and dermal route, as well as via the combined routes, are clearly below 1.

10. RISK CHARACTERISATION RELATED TO COMBINED EXPOSURE

10.1. Human health

NOTE: When relevant select the combinations of exposure scenarios which could result in simultaneous exposure of humans and report the outcome of the assessment here. <<<

10.1.1. Workers

10.1.2. Consumer

10.2. Environment (combined for all emission sources)

10.2.1. All uses (regional scale)

10.2.1.1. Total releases

The total releases to the environment from all the exposure scenarios covered are presented in the table below. This is the sum of the releases to the environments from all exposure scenarios addressed.

Table 19. Total releases to the environment per year from all life cycle stages:

Release route	Total releases per year
Water	0 kg/year
Air	3.5 kg/year
Soil	0 kg/year

10.2.1.2. Regional exposure

Environment

The regional predicted environmental concentration (PEC regional) and the related risk characterisation ratios when a PNEC is available are presented in the table below.

The PEC regional have been estimated with EUSES.

Table 20. Predicted regional exposure concentrations (Regional PEC)

Protection target	Regional PEC	RCR
Freshwater	1.598E-8 mg/L	< 0.01
Sediment (freshwater)	6.064E-8 mg/kg dw	< 0.01
Marine water	1.616E-9 mg/L	< 0.01
Sediment (marine water)	6.21E-9 mg/kg dw	< 0.01
Air	1.052E-10 mg/m³	
Agricultural soil	2.229E-8 mg/kg dw	< 0.01

The RCRs for all environmental compartments are clearly below 1.

Man via environment

The exposure to man via the environment from regional exposure and the related risk characterisation ratios are presented in the table below. The exposure concentration via inhalation is equal to the PEC air.

Table 21. Regional exposure to man via the environment

Route	Regional exposure	RCR
Inhalation	1.052E-10 mg/m³	< 0.01
Oral	3.368E-9 mg/kg bw/day	< 0.01
Combined routes		< 0.01

The RCRs for exposure of man via the environment via the inhalation and dermal route, as well as via the combined routes, are clearly below 1.

10.2.2. Local exposure due to all wide dispersive uses

Not relevant as there are not several wide dispersive uses covered in this CSR.

10.2.3. Local exposure due to combined uses at a site

NOTE: When relevant select the combinations of exposure scenarios which could result in simultaneous exposure of environment and report the outcome of the assessment here. <<<