CHEMICAL SAFETY REPORT

Non-confidential report

Legal name of applicant(s):	Novartis Ringaskiddy Limited IE Ringaskiddy, County Cork
Submitted by:	Novartis Ringaskiddy Limited IE Ringaskiddy, County Cork
Substance:	Diglyme (Bis(2-methoxyethyl)ether), EC No: 203-924-4; CAS No: 111-96-6
Use title:	Use of diglyme as solvent in the manufacturing process of an intermediate for further conversion into a pharmaceutical compound used in medicinal products for treatment of respiratory diseases
Use number:	1

Part 1-8 are not part of the Non-confidential report.

DECLARATION

We, Novartis Ringaskiddy Limited request that the information blanked out in the "public version" of the Chemical Safety Report is not disclosed. We hereby declare that, to the best of our knowledge as of today (20.11.2015) the information is not publicly available, and in accordance with the due measures of protection that we have implemented, a member of the public should not be able to obtain access to this information without our consent or that of the third party whose commercial interests are at stake.

Signature:

Jimmy O'Leary

Head of HSE

Novartis Ringaskiddy Limited

Date, Place:

20 Nov 2015
Ringaskiddy

9 EXPOSURE ASSESSMENT (and related risk characterisation)

9.0 Introduction

9.0.1 Overview of uses and exposure scenarios

Use of diglyme as a process solvent takes place at a Novartis EU pharmaceutical production site. Diglyme is used in exactly one manufacturing step in the synthesis of an intermediate for an active pharmaceutical ingredient (API). The intermediate is identified by its product code [redacted], after which the process step in question is named. For details on the technical function and the importance of diglyme in this process the reader is referred to the Analysis of Alternatives (AoA).

The entire [redacted] process is performed automatically in a closed system, with no significant opportunity for exposure of workers or release to the environment. Opportunities for exposure are however given during the following steps that require manual intervention:

1) Diglyme charging: The solvent is transferred from transport drums into the closed system (head tank)
2) CP1 (control point 1) sampling: A small volume of the reaction solution is sampled for the purpose of process and quality control, and transferred to the laboratory
3) Quality control: Analytical processing of the CP1 sample by laboratory staff
4) Waste handling: Transfer of bulk solvent waste (containing diglyme in the lower percent range) from closed waste storage tanks to road tankers

Any other process steps do not require handling of any materials by personnel. Since the manufacturing system is completely closed there is no significant opportunity for exposure or release to the environment. Transfer of solvent and/or reaction solution between vessels takes place via fixed piping, i.e. within the closed system and hence does not constitute a separate process step that would need to be evaluated.

Preventative maintenance

The entire equipment is serviced on a regular basis (preventative maintenance) according to maintenance plans (MPs) for every component of the facility that requires regular maintenance (Functional Location Number, FLOC). Preventative maintenance does not entail any exposure to diglyme, since it is performed prior to the production campaign on equipment devoid of any process chemicals. Therefore, preventative maintenance ensures proper functioning and pressure tightness of the equipment and a maximum level of containment, safeguarding against exposure to diglyme during its use in the synthesis process. An outline of preventative maintenance is given as follows:

MPs are formulated for each FLOC by maintenance engineers. Prior to the FLOCs going into service, all the required MP's are identified and scheduled by the maintenance planner. Technical procedures are detailed by a dedicated SOP. Performance and completion of all required MPs is supervised by the maintenance coordinator. The maintenance procedure is documented in the computerised maintenance management system.

Furthermore, prior to start of charging and production the equipment is subjected to a pressure and integrity test to ensure full leak-tightness of the system. Charging and production must not start without the integrity test being passed.

The whole occupational exposure scenario for the [redacted] process can be broken down into the following contributing scenarios (including those with no opportunity for exposure, and those with potential for exposure above):

Diglyme charging

Diglyme is charged via containment booth 552.719 into the head tank 552.212. The containment booth is designed as a glove box with fixed gauntlets (see Figure 1), and is equipped with an integrated exhaust ventilation (laminar flow booth design). A 200 L drum is placed in the booth, the containment door is closed, the exhaust ventilation started, and the drum is opened in the enclosed system. A dip pipe with attached flexi-hose, which remains in the enclosure, is placed into the drum. The drum is pumped using a fixed diaphragm pump via hard pipeline which is flanged with gaskets. During the charging of diglyme air/nitrogen is sucked into the drum. When the drum is empty, the suction lance is removed, suction valves are closed, and the lance and all lines are blown clear with nitrogen; the lance is placed into the storage drum (cf. Figure 2). The empty diglyme drum is sealed (lid replaced) in the closed booth, and then the booth opened, the drum sealed in double liner and sent to off-site incineration. A second drum is filled into head tank in the same manner. [redacted]

[redacted]

It should also be noted that diglyme is a flammable liquid that may release explosive vapours. For this reason, strict safety measures apply (earthing of movable vessels and devices, use of explosion-proof equipment, strict avoidance of spills, careful handling of the solvent). Operators are advised to maintain a high containment level. These measures significantly contribute to minimisation of operator exposure. Operators receive specific training for this task.

The figures on volumes and frequency of charging above apply to typical production campaigns. However, for the 2014 campaign, that serves as a representative example for developing the exposure scenarios for the current CSR, all drums of diglyme were charged into the head tank on one specific day. Accordingly, the stock for the entire campaign was charged at one single event. This is considered to be a worst-case of peak exposure in terms of both workplace exposure and release to the environment via exhaust air.

Figure 1: Containment booth

Figure 2: Suction lance inside the containment booth, with connected piping and storage drum

The operator wears the following PPE:

- Compressed airline hood (Respirex) conforming to EN 270:1995 and EN 467:1995, with an experimentally confirmed protection factor of ≥ 1000 (worst case)
- Disposable chemical protective suit (e.g. Tyvek)
- Chemical resistant gloves (barrier gloves (Ansell) and nitrile gloves (Best N-Dex) underneath in double layer)

The exhaust ventilation is run until 20 min after termination of the charging operation.

Off-gas treatment and release to the environment: The extract system for containment booth discharges to atmosphere. However, in view of the small aperture of the drums (max. 7 cm diameter) and the low volume of solvent handled (in total 400 L per event) any losses to the atmosphere are expected to be minimal. In a simplistic and conservative approach, the amount of diglyme emitted via exhaust air can be estimated according to the release factors given in the TGD (2003), Appendix I, Table A1.1: [redacted]. This is a very conservative calculation as material is sucked in: Air/nitrogen sucked into the drum during charging operation. The calculated release represents one-time peak exposure. [redacted].

Reaction phase (synthesis)

[redacted]

This process is fully automated, taking place in a completely closed reactor. Planned maintenance is scheduled prior to the production campaign: All scheduled maintenance during the timeframe of the production campaign is reviewed and performed prior to production start-up. Equipment setup and pressure/integrity testing is performed prior to production. Also the filtering apparatus is fully contained and any generated vapours are removed by an integrated ventilation system. Manual interference is not required. The process is supervised by remote control from a control room. Process synthesis tasks for operators vary but may involve equipment checks within the production areas, monitoring of equipment from the control room or conducting process tasks for other stages of the [redacted] process which do not involve diglyme. The operator does not have any direct contact with diglyme during process synthesis tasks. Therefore, the technical setup effectively prevents exposure of personnel to diglyme.

In the event of an emergency breakdown, a safe system of work is in place to assess exposure and to ensure that the appropriate measures are in place to ensure no impact to human health and/or environment.

Releases to the environment from this process step are not expected due to complete containment of the process.

CP1 (control point 1) sampling, including transfer to the laboratory

Upon completion of the reaction a sample is drawn from the reactor using a closed propriety process sampling system: First of all, the area is closed off prior and during sampling so that only the affected operator has access. Operation of the process sampler involves first connecting the sample jar to the sampling point which is located within a closed box. An intermediate chamber is evacuated and filled with the 50 mL of reaction mixture which is then decanted into the 100 mL sample jar. During the filling of the sample jar with a fixed volume a splash barrier/guard is in effect, which prevents splashing during sampling. Exposure is contained at all times except for a brief period when the sample jar is removed from the sampling point and sealed with the lid. The sample jar is transported to the laboratory using a specially designed carrier. Operators have to wear PPE in the form of n-dex nitrile gloves (inner) and solvex/barrier gloves (outer), and have to take a specified walkway to the lab. Outer gloves are removed after sampling. The sample jar volume is 100 mL, filled with 50 mL reaction mixture.

CP1 sampling normally takes approximately 5 minutes. Total potential exposure time, including preparatory activities prior to withdrawal of the sample, and transport to the laboratory can add up to maximally 20 minutes, i.e. the time needed for transport to the laboratory is 15 minutes at maximum.

Environmental release from this task is negligible, due to the small volume (ca. 50 mL) sampled and the tight connection between sample jar and the filler neck.

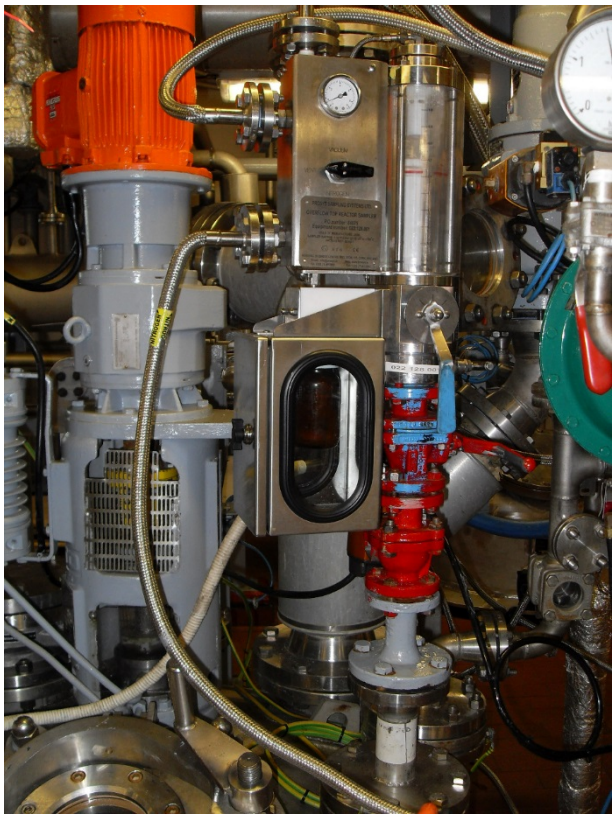

Figure 3: Process sampler for CP1 sampling

Quality control – laboratory analysis

Analysis of the CP1 sample is conducted in the QC laboratory using high performance liquid chromatography (HPLC). The CP1 sample is opened in a fume cupboard and 50-150 µl is removed using a pipette and mixed in a burette with other solvents in preparation of the HPLC sample solution. The sample solution is then run on the HPLC system for a period of up to 3 hours. Once the HPLC run is completed the remaining CP1 sample is poured into a waste container in a fume hood. Waste from the laboratory is disposed of by onsite incineration.

Environmental release from this task is negligible, due to the small volume processed.

Waste transfer

[redacted]

The waste tank 652.234, which is inertised with nitrogen and exhaust vapours are directed to onsite incineration, receives bulked solvent waste from various processes with diglyme accounting for approximately 1.5 % (final concentration). Liquid waste is transferred to a road tanker and sent to off-site incineration as hazardous waste approximately once per month. Road tanker loading from waste tank 652.234 is carried out north of the control room of the wastewater treatment plant, in the tanker laydown area. The road tanker has been flushed clean and has not been used to deliver diglyme to the site. During the placing of the filling arm into the road tanker no waste is released from tank 652.234. The filling operation is conducted remotely from the control room by the waste operators. The greatest likelihood of exposure of the operator is during removal of the loading arm prior to closing up the tanker, the closing of the hatch and while taking a sample from the tanker. The loading arm is controlled pneumatically so the operator is not exposed to waste while operating this. The loading arm is designed as a cone that is inserted into the charging hole, resulting in a sealed connection that minimises any release of solvent vapours.

Personal protective equipment consists of a full-face mask (EN 136) with combined filter (EN 14387) and solvex/n-dex gloves. This respiratory protective equipment combination gives an assigned protection factor of 20. The tanker is out of bounds and other personnel are not permitted in the area during loading operations. Within the QAB process there are 4 waste streams entering the waste tank:

[redacted]

Tonnage information:

The annual tonnage band is 1-10 tonnes/year.

[redacted]

Tonnage supplied per market sector:

Not relevant for this application; this CSR has been prepared in the context of an individual application for authorisation of one specific use of diglyme. The current CSR covers only this particular use hence market sector-wide tonnages need not be considered.

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

Table 1. Overview of exposure scenarios and contributing scenarios

Identifiers*)	Market Sector	Titles of exposure scenarios and the related contributing scenarios	Tonnage (tonnes per year)
IW-1	Pharmaceuticals	Use as a solvent in the manufacture of APIs: • Environmental contributing scenario 1 • Worker contributing scenario 1 – diglyme charging (PROC 8b) • Worker contributing scenario 2 – use as solvent in chemical synthesis (PROC 1) • Worker contributing scenario 3 – CP1 sampling (PROC 9) • Worker contributing scenario 4 – quality control in the laboratory (PROC 15) • Worker contributing scenario 5 – waste handling (PROC 8b)	1-10
*) Industrial end use at site: IW-#			

9.0.2 Introduction to the assessment

9.0.2.1 Environment

Scope and type of assessment:

Diglyme has been 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: Diglyme carries a harmonised classification of "Repr. 1B, H360FD (may damage fertility; may damage the unborn child)" according to the CLP-Regulation (EC) No 1272/2008. Therefore, this classification of the substance(s) in Regulation (EC) No 1272/2008 shows that the substance meets the criteria for classification as toxic for reproduction in accordance with Article 57(c) of REACH.

The current CSR and the associated exposure scenario are tailored to supporting the application for authorisation of bis(2-methoxyethyl)ether (diglyme) for its use as solvent in the manufacture of active pharmaceutical ingredients. 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 assessment of human and environmental exposure and the potentially associated risks.

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. Accordingly, only the human health risks related to the classification of diglyme as a reproductive toxicant are assessed in the current CSR. The dominating health effect resulting from the intrinsic hazardous properties of diglyme is the potential to cause adverse effects to the reproductive system and to harm the unborn child. Any route of exposure (inhalation, dermal, oral) may be relevant for evaluating health risks, with only the dermal and inhalation route being relevant for risks arising from occupational exposure. Evaluation of any potential hazards to the environment is not required within the framework of this authorisation application, as outlined in Table 7. 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 as hazardous waste by a licenced contractor – also see below) emissions of diglyme to the aquatic environment are effectively prevented.

Emissions to air cannot be completely excluded in view of the (albeit 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 (ventilation of the containment booth, see above).

Filling of road tankers takes place outdoors. Whereas emissions to air could in principle occur during this phase, the tightly fitting filler pipe (cone shaped sealing) prevents release of vapours. Emissions to the environment during this phase are therefore considered to be negligible. These emission control measures, in combination with remote control of the loading arm and the filling procedure, are also effective for minimising operator exposure (see worker contributing scenario, section 9.1.6).

In conclusion, emissions resulting from ventilation of the containment booth are estimated in a worst-case approach. The scope and type of the assessment for the pathway "man via the environment" is discussed in section 9.0.2.2.

Table 2. Type of risk characterisation required for the environment

Protection target	Type of risk characterisation	Hazard conclusion
Freshwater	Not relevant	–
Sediment (freshwater)	Not relevant	–
Marine water	Not relevant	–
Sediment (marine water)	Not relevant	–
Sewage treatment plant	Not relevant	–
Air	Not relevant	–
Agricultural soil	Not relevant	–
Predator	Not relevant	–

Comments on assessment approach:

In accordance with Regulation (EC) No 1907/2006, Article 62(4)(d) risks to the environment need not be considered.

9.0.2.2 Man via environment

Scope and type of assessment:

With reference to section 9.0.2.1, 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.

Within the current CSR, emissions to air are estimated based on worst-case assumptions: As already elaborated in section 9.0.1 – diglyme charging) the release factor is adopted from the TGD (2003), Appendix I, Table A1.1 (release factor 0.0001) and Table B2.8 (fraction of the main source = 1.0). The number of release days is specified following the applicant's specification of the production process:

Airborne concentrations (PEClocal in a 100 m diameter around the emission source) and PEC regional are estimated using EUSES 2.1.2 (see Appendix 1 for the full EUSES report).

Table 3. Type of risk characterisation required for man via the environment

Route of exposure and type of effects	Type of risk characterisation	Hazard conclusion (reference DNEL, RAC/33/2015/08 rev 1)
Inhalation: Local long-term	Quantitative	DNEL = 0.30 mg/m³
Oral: Systemic long-term	Not needed	–

Comments on assessment approach:

The risk assessment for humans exposed via the environment is restricted to inhalation of airborne residues of diglyme. Although in the Annex XV dossier a DNEL for exposure of consumers via the dermal route was derived, this path is not relevant when considering exposure via the environment. Vapours may either be inhaled, or condensed and subsequently be accumulated in the food chain (oral exposure). However, in view of the substance's properties (partition coefficient log $P_{ow} = -0.36$) diglyme is not expected to accumulate in the food chain hence inhalation is the only relevant pathway for assessing exposure of humans via the environment.

9.0.2.3 Workers

Scope and type of assessment:

Table 4. Type of risk characterisation required for workers

Route	Type of effect	Type of risk characterisation	Hazard conclusion (reference DNEL, RAC/33/2015/08 rev 1)
Inhalation	Systemic long-term	Quantitative	DNEL = 1.68 mg/m³
	Systemic acute	Not needed	None identified
	Local long term	Not needed	None identified
	Local acute	Not needed	None identified
Dermal	Systemic long term	Quantitative	DNEL = 0.24 mg/kg bw/d
	Systemic acute	Not needed	None identified
	Local long term	Not needed	None identified
	Local acute	Not needed	None identified
Eye	Local	Not needed	None 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 dominating health effects resulting from the intrinsic hazardous properties of diglyme are:

- Impairment of male reproductive organs
- Developmental toxicity, most notably increased incidence of resorption and a higher risk of major malformations

The DNELs presented in Table 9 were derived by the Member State Competent Authorities (MSCAs) responsible for the Annex XV dossier on the basis of the developmental and reproductive toxicity studies in which the above effects were identified. Based on the dose-response relationships, 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 exposure were preferably calculated using the Advanced REACH Tool (ART) version 1.5[1], with specification of activities and input parameters as detailed in the respective contributing exposure scenarios below. ART is much better suited for realistic, activity-based exposure modelling than the default model ECETOC TRA. Exceptionally, however, ECETOC TRA was used for estimating inhalation exposure during laboratory analysis (PROC 15) since ART is less suitable for mapping laboratory activities.

Exposure estimates generated by ART v1.5 are given as the 90th percentile of the exposure distribution, in accordance with the ECHA-guidance on "information requirements and chemical safety assessment, chapter R.14: Occupational exposure estimation", sub-chapter R14.4.

Inhalation exposure was measured during the 2014 production campaign. Aerial samples were drawn during all of the five tasks identified above. Exposure measurements were conducted as personal samples using active samplers (SKC sidekick sampling pumps). Each pump was calibrated directly prior to and post sampling. Diglyme was absorbed onto coconut shell charcoal tubes (SKC Product Code: 226-09). Analysis of the sampled tubes was conducted by Bureau Veritas North America, which is an accredited industrial hygiene laboratory. The samples were desorbed in methylene chloride/methanol (95:5) and analysed using gas chromatography with flame ionisation detector (GC/FID). Measured exposure values constitute potential exposure, i.e. not taking into account PPE. Therefore, measured values were corrected by the respective protection factors for the used PPE, where appropriate (see contributing scenarios below for details). Measured values are used as supporting evidence of modelled exposure estimates in this CSR.

Estimation of dermal exposure was performed using ECETOC TRA by default, being the standard model for dermal exposure assessment under REACH. Tier 2 dermal exposure modelling, where necessary, was performed using RISKOFDERM v2.1. This was the case with CP1 sampling (WCS 3, PROC 9), and waste transfer (WCS 5, PROC 8b). ECETOC TRA returns extremely conservative dermal exposure estimates with these PROCs, not adequately reflecting substance properties and the level of protection provided by the operational conditions and risk management measures in place. RISKOFDERM, by contrast, allows more targeted modelling of the level of dermal contact and is an accepted tool collaboratively developed by several EU member states' competent authorities. With the remaining WCS, in consideration of the consistently high level of occupational safety in the [redacted] process at Novartis Ringaskiddy, the relatively simplistic approach of ECETOC TRA is considered to be appropriate.

Comments on assessment approach related to physicochemical hazard:

Not relevant – physicochemical hazards are not subject of this chemical safety report.

General information on risk management related to toxicological hazard:

Exposure of workers handling diglyme in the course of the [redacted] manufacturing process is restricted to the lowest possible level:

There is no open handling of diglyme at any stage of the process. Details on the technical procedures and safety measures are described in section 9.0.1. A brief summary of the risk management measures related to the toxicological hazard is given as follows:

- Diglyme charging from drums into the head tank is performed using a closed laminar flow booth in glove box design, strictly operated using the integrated gauntlets; diglyme is charged by vacuum using a suction

[1] https://www.advancedreachtool.com/

lance; PPE of operators consists of chemical protective suit, compressed airline hood, and solvent resistant protective gloves (double layer: outer PE barrier glove, inner n-dex nitrile)

- Use of diglyme in [redacted] synthesis takes place in a completely closed reactor that is connected to the head tank and downstream vessels by hard piping; therefore, there is no possibility of exposure; filtration of the finished [redacted] 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
- CP1 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; PPE for operators consists of solvent-resistant protective gloves (double layer: outer PE barrier glove, inner n-dex nitrile)
- All activities for quality control (analysis by HPLC) are performed in a fume cupboard, the volumes handled are very small (50-150 µL), PPE consists of solvent-resistant protective gloves
- Solvent waste is transferred from the aforementioned waste tank to a road tanker and sent to off-site incineration; waste transfer takes place outdoors using a movable and telescopic loading arm equipped with a conical sealing structure that ensures tight fitting into the tanker manhole; the loading arm is operated pneumatically by remote control; contact to potentially contaminated surfaces is strictly avoided; during operation of the loading arm and sampling PPE in the form of work clothing, solvent resistant protective gloves (Solvex) and RPE (full face mask (EN 136) with combined filter (EN 14387)) is mandatory.

Overall, it has to be noted that exposure controls related to the use of diglyme as a process solvent at Novartis Ringaskiddy are very stringent. The measures described in the current section and in the worker contributing scenarios (sections 9.1.2 to 9.1.6) ensure strict avoidance of occupational exposure to diglyme and go far beyond the default risk management options provided in the exposure estimation models (ECETOC TRA, ART, RISKOFDERM). Therefore, model-based exposure estimates, even when corrected for risk management measures actually implemented at Novartis Ringaskiddy, are still extremely conservative. Accordingly, the risk characterisation for the use of diglyme as solvent in API manufacture still significantly overestimates risks, although all process steps are clearly identified as safe (RCR << 1.0). Therefore, based on the exposure scenarios and risk characterisations presented in the following, there are no unacceptable risks resulting from the use of digylme as solvent in the manufacture of an active pharmaceutical ingredient.

General information on risk management related to physicochemical hazard:

Not relevant – physicochemical hazards are not subject of this chemical safety report.

9.0.2.4 Consumers

Scope and type of assessment:

The application for authorisation is restricted to one specific industrial use only. Consumer uses are not subject of the current CSR.

9.1 Exposure scenario 1: Use at industrial site – Solvent for API manufacturing

Sector of use:
SU 9, Manufacture of fine chemicals

Environment contributing scenario(s):	
Solvent for API manufacturing	ERC 7
Worker contributing scenario(s):	
Diglyme charging	PROC 8b
[redacted] synthesis	PROC 1
CP1 sampling and transport to laboratory	PROC 9
Quality control	PROC 15
Waste transfer to road tanker	PROC 8b

9.1.1 Environmental contributing scenario 1: Solvent for API manufacturing

9.1.1.1 Conditions of use

Amount used, frequency and duration of use (or from service life)
• Daily use at site: [redacted] *In a worst case approach, it is assumed that the amount of diglyme required for one production campaign ([redacted]) is charged on one single day. Consequently, this is a non-recurring event hence the release pattern is intermittent.*
• Annual use at a site: 1-10 tonnes/year
• Percentage of EU tonnage used at regional scale: = 100 %
Conditions and measures related to sewage treatment plant
• Municipal STP: Yes [Effectiveness Water: 100%]
• Discharge rate of STP: >= 2E3 m3/d
• Application of the STP sludge on agricultural soil: Yes
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
• 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 5. Local releases to the environment

Release	Release factor estimation method	Explanation / Justification
Water	Release factor (Site-specific release factor)	**Initial release factor:** 0% **Final release factor:** 0% **Local release rate:** 0 kg/day **Explanation / Justification:** The system is completely closed. Any liquid waste is submitted to a solvent waste storage tank via fixed piping, and then sent to off-site incineration via road-tanker. Release to wastewater is strictly avoided.
Air	Release factor (TGD (2003))	**Initial release factor:** 0.01% **Final release factor:** 0.01% **Local release rate:** 0.15 kg/day **Explanation / Justification:** The only emission source is exhaust air from the containment booth used for charging (see section 9.0.1 above). In a simplistic and conservative approach, the amount of diglyme emitted via exhaust air can be estimated according to the release factors given in the TGD (2003), Appendix I, Table A1.1: The equipment used is dedicated equipment (category Ic); diglyme has a vapour pressure of 60 Pa at 20 °C; the resulting release factor to air is 0.0001 (0.01 %).
Soil	Release factor (Site-specific release factor)	**Final release factor:** 0% **Explanation / Justification:** The system is completely closed. Any liquid waste is submitted to a solvent waste storage tank via fixed piping, and then sent to off-site incineration via road-tanker. Release to the environment is strictly avoided.

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

The exposure concentrations and the excess risk are reported in the following table.

Table 6. Exposure concentrations and risks for the environment (and man via the environment)

Protection target	Local concentration (Clocal, PEC)	RCR
Freshwater	0 mg/L	Not required
Marine water	0 mg/L	Not required
Air	1.142E−07 mg/m³	Not required
Agricultural soil	5.448E−08 mg/kg dw	Not required
Man via environment – inhalation	Local PEC: 1.142E−07 mg/m³	3.8E−07

Risk characterisation (minimisation of emission/exposure)

A risk characterisation for the environment is not required in the context of application for authorisation, since the effects giving reason to inclusion into REACH Annex XIV are exclusively health-related.

The risk for the general population exposed via the environment (inhalation of any vapours potentially emitted and leading to exposure in the vicinity of the emissions source) is controlled, with an RCR of 3.8E−07 (see Table 11)

9.1.2 Worker contributing scenario 1: Diglyme charging (PROC 8b)

9.1.2.1 Conditions of use

The process of diglyme charging, including all implemented risk management measures, PPE, etc., is described in detail is section 9.0.1 above. Inhalation exposure is modelled using the Advanced REACH Tool (ART) v1.5 and compared to measured data. Since there was one charging event in the 2014 production campaign only two personal samples could be measured. Dermal exposure is estimated using ECETOC TRA, as the default worst-case modelling tool.

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 1 hour	TRA Worker v3
Technical and organisational conditions and measures	
• Containment: Semi-closed process with occasional controlled exposure	TRA Worker v3
• Local exhaust ventilation (for dermal): yes [Effectiveness Dermal: 95%] *In view of the design of the laminar flow booth, resulting in complete separation of the operator from the source of exposure, it is considered to be fully justified to allow for LEV as a mitigating factor also for dermal exposure. The model estimate represent a vast overestimation anyway, in view of the safety measures applied (containment booth in glove box design, double layer of protective gloves, suction lance for minimisation of spills, chemical protective suit).*	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
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 Worker v3
Other conditions affecting workers exposure	
• Skin surface potentially exposed: Two hands (960 cm²)	TRA Worker v3

9.1.2.2 Exposure and risks for workers

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

Table 7. Exposure concentrations and risks for workers

Route of exposure and type of effects	**Exposure concentration**	**Risk characterisation**
Inhalation, systemic, long-term	**6.6E-6 mg/m³** (External Tool (ART 1.5)) **Additional data not used for RCR:** < 3.5E-4 mg/m³ (Measured HH (Measured exposure, diglyme charging, values < LOQ)	RCR < 0.01
Dermal, systemic, long-term	**0.034 mg/kg bw/day** (TRA Worker v3)	RCR = 0.143
Combined routes, systemic, long-term		RCR = 0.143

Remarks on exposure data

External Tool (ART 1.5)

- Inhalation, systemic, long-term:

Scenario details	
Number of activities	1
Total duration (mins)	480
Nonexposure period (mins)	440
Details for activity diglyme charging	
Emission sources:	Near field
Duration (mins):	40
Near-field exposure	
Operational conditions	
Substance emission potential	
Substance product type	Liquids
Process temperature	293 K
Vapour pressure	60 Pa
Liquid mole fraction	1
Activity coefficient	1
Activity emission potential	
Activity class	Activities with relatively undisturbed surfaces (no aerosol formation)
Situation	
Open surface	< 0.1 m²
Surface contamination	
Process fully enclosed?	No
Effective housekeeping practices in place?	Yes
Dispersion	
Work area	Indoors
Room size	3000 m³
Risk Management Measures	
Localised controls	
Primary	Low specification glove box (99.90 % reduction)
Secondary	Other enclosing hoods (90.00 % reduction)
Dispersion	
Ventilation rate	1 air change per hour (ACH)

Predicted exposure is given as the 90th percentile full-shift exposure.

Measured HH (Measured exposure, diglyme charging)

- Inhalation, systemic, long-term:
  Number of measured data points: 2
  Measurements of airborne residues during diglyme charging were specifically conducted with the aim of supporting this application for authorisation. In view of the limitations imposed by the production schedule (see section 9.0.1 above) there was only one opportunity for air sampling. Two operators were fitted with active samplers. No diglyme was detected, i.e. analytical values were below the LOQ of 0.35 mg/m³ (potential exposure, not taking into account PPE). Considering the compressed air hood with a protection factor, this translates into a personal exposure value of < 3.5E−04 mg/m³. Since only 2 samples could be taken, the LOQ divided by the protection factor is adopted as the relevant exposure value. No further adaptations (e.g. assigning ½ LOQ as the measured value) are made. In view of the sample size (n = 2) the measured values are used as supportive information, confirming low exposure as predicted by the ART model.

9.1.3 Worker contributing scenario 2: [redacted] synthesis (PROC1)

9.1.3.1 Conditions of use

Process synthesis takes place in a completely closed reactor. Tasks for operators vary but may involve equipment checks within the production areas, monitoring of equipment from the control room or conducting process tasks for other stages of the [redacted] process which do not involve diglyme. The operator does not have any direct contact with diglyme during process synthesis tasks. Since operators perform the aforementioned equipment checks only

occasionally and spend the largest part of a work shift in the control room (e.g. with paper work) the actual exposure time is less than one hour. Inhalation exposure is estimated both using ART and based on measured data. For estimation of dermal exposure ECETOC TRA is used, due to lack of other suitable tools. In view of the high level of containment (completely closed system, with no possibility of surface contamination by the reaction solution) the TRA generated exposure value is a vast overestimate. In reality, the likelihood and level of dermal exposure is negligible.

For these reasons, the inhalation exposure estimates provide below are related to a full shift. Worker activities cover supervision of the chemical reaction remotely from the control room, and occasional equipment checks in the production hall. The inhalation exposure estimate is based on measurements (personal sampling using active sampling pumps and activated carbon tubes) and is given as the 8 hour time-weighted average.

Dermal exposure, by contrast can potentially only occur during the occasional equipment checks. Exposure duration for modelling (TRA Worker v3) is therefore set at < 1 h, as a worst-case.

Planned maintenance is scheduled prior to the production campaign: All scheduled maintenance during the timeframe of the production campaign is reviewed and performed prior to production start-up. Equipment setup and pressure/integrity testing is performed prior to production. Also the filtering apparatus is fully contained and any generated vapours are removed by an integrated ventilation system. Filtering is part of the synthesis described by the current exposure scenario (PROC 1). Manual interference is not required. Therefore, the technical setup effectively prevents exposure of personnel to diglyme.

Solvent washing ensures effective removal of diglyme from the final product. Quality control data show that the final product does not contain any detectable residues of diglyme.

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 1 hour	TRA Worker v3
Technical and organisational conditions and measures	
• Containment: Closed system (minimal contact during routine operations)	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
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%] *For any activities involving contact with equipment surfaces, use of solvent-resistant protective gloves is required.*	TRA Worker v3
Other conditions affecting workers exposure	
• Skin surface potentially exposed: One hand face only (240 cm²)	TRA Worker v3

9.1.3.2 Exposure and risks for workers

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

Table 8. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**< 0.22 mg/m³** (Measured HH (Measured exposure, synthesis), values < LOQ) **Additional data not used for RCR:** 0.011 mg/m³ (TRA Worker v3)	RCR < 0.131
Dermal, systemic, long-term	**0.002 mg/kg bw/day** (TRA Worker v3)	RCR < 0.01
Combined routes, systemic, long-term		RCR < 0.14

Remarks on exposure data

Measured HH (Measured exposure, synthesis)

- Inhalation, systemic, long-term:
  Number of measured data points: 10
  Personal diglyme exposure to operators was measured on ten occasions during process synthesis, with six different operators sampled. The sampling periods and tasks conducted by the operators, which varied for each sample taken, ranging between 131 and 231 minutes. Average diglyme exposures, given as the 8 hour time-weighted average, were below the detection limit of the sampling and analysis method for all ten samples. Due to the variation in sampling periods the limit of quantitation for exposure ranged from < 0.0.24 mg/m³ to < 0.44 mg/m³. The measured exposure value for risk assessment is derived in a worst-case approach as follows: Since all samples were below the LOQ, statistical derivation based on an exposure distribution is not feasible. Instead, the highest (least reliable) value from the above range is taken as the point reference, i.e. measured exposure was always < 0.44 mg/m³ (highest confirmed LOQ). As a commonly accepted principle, half of the LOQ is adopted as the measured exposure concentration when the analyte could not be quantified, i.e., 0.22 mg/m³. This value is taken forward to the risk assessment.

9.1.4 Worker contributing scenario 3: CP1 sampling and transport to laboratory (PROC 9)

9.1.4.1 Conditions of use

This task actually consists of two phases that are assessed in combination, since the operator performs the phases of sample drawing and transport to the QC laboratory in succession (see section 9.0.1 above for details). This is not exactly reflected by the selected process category (PROC 9) since the transport to the lab does not fit within the default use descriptor concept. However, the definitive inhalation exposure estimation is not performed using ECETOC TRA (which depends on PROCs) but instead uses ART as an external tool, and also measured data as supportive information. Assessment of dermal exposure relies on ECETOC TRA which is known to generate very conservative dermal exposure estimates. During transport, there is absolutely no dermal contact to any object that could potentially be contaminated with diglyme (use of a dedicated carrier is mandatory) so that it is justified to ignore the transport phase for dermal exposure assessment.

9.1.4.2 Exposure and risks for workers

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

Table 9. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.008 mg/m³** (External Tool (ART 1.0)) **Additional data not used for RCR:**	RCR < 0.01

Route of exposure and type of effects	Exposure concentration	Risk characterisation
	< 0.41 mg/m³ (Measured HH (Measured exposure, CP1 sampling), values < LOQ, thus ½ LOQ is reported)	
Dermal, systemic, long-term	**0.016 mg/kg bw/day** (External Tool (Riskofderm 2.1))	RCR = 0.067
Combined routes, systemic, long-term		RCR = 0.072

Remarks on exposure data

External Tool (ART 1.5)

- Inhalation, systemic, long-term:

Scenario details

Number of activities	2 (sample withdrawal, transport to lab)
Total duration (mins)	480
Nonexposure period (mins)	460

1) Details for activity CP1 sampling

Emission sources:	Near field
Duration (mins):	5
Near-field exposure	
Operational Conditions	
Substance emission potential	
Substance product type	Liquids
Process temperature	293 K
Vapour pressure	60 Pa
Liquid mole fraction	1
Activity coefficient	1
Activity emission potential	
Activity class	Falling liquids
Situation	Transfer of liquid product with flow of 0.1–1 l/minute
Containment level	Open process
Loading type	Splash loading, where the liquid dispenser remains at the top of the reservoir and the liquid splashes freely (**Comment:** ART provides only for either "splash loading" or "submerged loading"; whereas splash loading is a correct description in terms of the model due to vertical filling, indeed no splashes are generated; a pre-defined volume of 50 mL is automatically filled at a low rate into the sample jar which is tightly connected to the filling nozzle within the closed sampling box, *cf.* Figure 3, page 21)
Surface contamination	
Process fully enclosed?	No
Effective housekeeping practices in place?	Yes
Dispersion	
Work area	Indoors
Room size	3000 m³
Risk Management Measures	
Localised controls	
Primary	Medium level containment (99.00 % reduction)
Secondary	No localized controls (0.00 % reduction)
Dispersion	
Ventilation rate	1 air change per hour (ACH)

2) Details for activity transport to QC laboratory

Emission sources:	Near field
Duration (mins):	15

Near-field exposure	
Operational Conditions	
Substance emission potential	
Substance product type	Liquids
Process temperature	293 K
Vapour pressure	60 Pa
Liquid mole fraction	1
Activity coefficient	1
Activity emission potential	
Activity class	Handling of contaminated objects
Situation	Activities with treated/contaminated objects (surface 0.1–0.3 m²)
Contamination level	Contamination < 10 % surface
Surface contamination	
Process fully enclosed?	No
Effective housekeeping practices in place?	Yes
Dispersion	
Work area	Indoors
Room size	3000 m³
Risk Management Measures	
Localised controls	
Primary	No localized controls (0.00 % reduction)
Secondary	No localized controls (0.00 % reduction)
Dispersion	
Ventilation rate	1 air change per hour (ACH)

Predicted exposure is given as the 90th percentile full-shift exposure, for the two activities combined.

Measured HH (Measured exposure, CP1 sampling)

- Inhalation, systemic, long-term:
  Number of measured data points: 10
  Personal exposure monitoring was conducted during CP1 sampling and transport of the sample to the QC laboratory. Ten samples were taken in total during which five different operators conducted the task. Average exposure to diglyme over a period of 44 minutes, ranging between 25 and 64 minutes. Only in the first CP1 sample diglyme was detected and quantified to be 0.86 mg/m³. This is an unexpectedly high value, considering the high level of containment of the CP1 sampling procedure. Contamination of the sample through contact with gloves or other clothing is a possible explanation for this unexpected result. This apparently positive sample is therefore regarded as an outlier. For the remaining nine of the ten samples taken exposure to diglyme was below the limit of quantitation (LOQ) of the sampling and analysis method. The air volume sampled varied for these nine samples depending on the duration of the CP1 sampling task and the corresponding exposure concentrations ranged from < 0.36 mg/m³ to < 0.82 mg/m³. The measured exposure value for risk assessment is derived in a worst-case approach as follows: Since all samples were below the LOQ, statistical derivation based on an exposure distribution is not feasible. Instead, the highest (least reliable) value from the above range is taken as the point reference, i.e. measured exposure was always < 0.82 mg/m³ (highest confirmed LOQ). As a commonly accepted principle, half of the LOQ is adopted as the measured exposure concentration when the analyte could not be quantified, i.e., 0.41 mg/m³. This value is adopted in lieu of a statistically derived 90th percentile. Accordingly, the value of 0.41 mg/m³ is taken forward to the risk characterisation.

External Tool (Riskofderm 2.1)

- Dermal, systemic, long-term:
  RISKOFDERM calculation and subsequent modifications:
  Module "filling, mixing or loading (DEO unit 1)"
  Quality of ventilation: Normal or good ventilation
  Frequency of skin contact with the contaminant: Rare contact
  Kind of skin contact with the contaminant: Light contact
  Type of product: Liquid
  Significant amounts of aerosols or splashes generated: No
  Level of automation: Manual task
  Use rate of product: 0.5 L/min
  Percentile for exposure distribution

Resulting exposure rate hands (90th percentile): 4.57 mg/min
Cumulative duration of task during a shift: 5 min
Exposure loading per shift hands: 22.8 mg
Correction for gloves (95 % protection): 1.14 mg
Correction for body weight (70 kg): 0.016 mg/kg bw/d

Note: During transport to the laboratory there is no dermal contact (sealed sample jar, no contaminated surfaces).

9.1.5 Worker contributing scenario 4: Quality control (PROC 15)

9.1.5.1 Conditions of use

Analysis of the CP1 sample is conducted in the QC laboratory using high performance liquid chromatography (HPLC). The CP1 sample is opened in a fume cupboard and 50- 150 µl is removed using a pipette and mixed in a burette with other solvents in preparation of the HPLC sample solution. The sample solution is stored in a sealed HPLC vial. HPLC analysis is performed by piercing the system's needle through the septum of the vial, extracting a defined quantity, and injection into the column head. The analysis, including system suitability check and evaluation of reference standards, is run on the HPLC system for a period of up to 3 hours. There is no exposure during the HPLC runtime and all analysis is performed within the instrument which is a fully closed system. Once the HPLC run is completed the remaining CP1 sample is poured into a waste container in a fume hood. Despite the maximum HPLC processing time of 3 hours, actual exposure of laboratory staff is significantly shorter: Potential exposure is limited to the phases of opening the sample jar, and the preparation of the sample solutions by withdrawing and aliquot with a pipette and transferring it to the HPLC sample vial. Finally, all residual material is disposed of into the waste container. All steps of this activity are performed in a fume cupboard. For the purpose of model-based exposure estimation (ECETOC TRA) it is therefore justified to assume an exposure period of less than 1 hour. Modelled exposure estimates will be generated by ECETOC TRA only since alternative tools like ART are not well suited for modelling laboratory activities. Measured data are available and will be used for exposure estimation.

	Method
Product (article) characteristics	
• Concentration of substance in mixture: Substance as such	TRA Worker v3
Amount used (or contained in articles), frequency and duration of use/exposure	
• Duration of activity: < 1 hour	TRA Worker v3
Technical and organisational conditions and measures	
• Containment: No	TRA Worker v3
• Local exhaust ventilation (for dermal): no [Effectiveness Dermal: 0%]	TRA Worker v3
• Occupational Health and Safety Management System: Advanced	TRA Worker v3
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 Worker v3
Other conditions affecting workers exposure	
• Skin surface potentially exposed: One hand face only (240 cm2)	TRA Worker v3

9.1.5.2 Exposure and risks for workers

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

Table 10. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**< 0.23 mg/m³** (Measured HH (Measured exposure, quality control), values < LOQ) **Additional data not used for RCR:** 0.559 mg/m³ (TRA Worker v3)	RCR < 0.137
Dermal, systemic, long-term	**0.017 mg/kg bw/day** (TRA Worker v3)	RCR = 0.071
Combined routes, systemic, long-term		RCR < 0.208

Remarks on exposure data

Measured HH (Measured exposure, quality control)

- Inhalation, systemic, long-term:
  Number of measured data point: 6
  Personal exposure to diglyme was measured during CP1 sample analysis in the QC Laboratory. Five different analytical chemists were sampled on the six occasions when CP1 sample analysis was surveyed. The average exposure was below the limit of quantitation (LOQ) of the sampling and analysis method for all six samples. The air volumes sampled varied for these six samples depending on the duration of the monitoring period (59–193 min); the corresponding exposure concentrations ranged from < 0.31 mg/m³ to < 0.46 mg/m³. The measured exposure value for risk assessment is derived in a worst-case approach as follows: Since all samples were below the LOQ, statistical derivation based on an exposure distribution is not feasible. Instead, the highest (least reliable) value from the above range is taken as the point reference, i.e. measured exposure was always < 0.46 mg/m³ (highest confirmed LOQ). As a commonly accepted principle, half of the LOQ is adopted as the measured exposure concentration when the analyte could not be quantified, i.e., 0.23 mg/m³, which is taken forward to the risk characterisation.

9.1.6 Worker contributing scenario 5: Waste transfer to road tanker (PROC 8b)

9.1.6.1 Conditions of use

[redacted], resulting in a final diglyme concentration of 1.5 %.

Filling the road tanker (25 tonnes solvent waste) takes approximately 2 hours. Consequently the transfer rate is approximately 200 kg/min and falls within the ART transfer rate range of 100–1000 L/min.

The waste is sent to off-site incineration by road tanker. Road tanker loading from waste tank 652.234 is carried out north of the waste water treatment plant control room in the tanker laydown area. The filling operation is conducted remotely from the control room by the waste operators. The tanker is exclusively used for disposal of solvent waste and is flushed clean before being filled. The likelihood of exposure during the various phases of waste transfer is assessed as follows: 1) Opening of the hatch and placing the loading arm into the tanker is not associated with any exposure since the solvent waste is still enclosed in tank 652.234; furthermore, the loading arm is controlled pneumatically so the operator does not come into contact with waste while operating it; therefore, this phase is not included in the model-based exposure estimation; 2) Automated solvent transfer, controlled remotely; far field exposure is possible, however unlikely; 3) Upon termination of waste transfer, removal of the loading arm and closing up the tanker; 4) Taking a sample from the tanker.

For model-based estimation of inhalation exposure using ART three relevant phases were thus defined in accordance with the above tasks: 1) Waste transfer by remote control (far field exposure, outdoors, is taken into account in a worst-case approach); 2) Removal of the loading arm and placing a bucket below the drop pipe (near field exposure); 3) Withdrawal of sample using a tanker sampling rod (near field exposure). Once the loading arm is placed in the manhole, the telescopic drop pipe is lowered until reaching the bottom of the tanker. This, in combination with the conical sealing structure, minimises any emissions that could lead to human or environmental exposure. Release of

waste from the storage tank 652.234 is not activated until the operator has returned to the control room to initiate the filling of the tanker. The total duration of waste transfer operations typically is 2 hours, plus approximately 5 minutes for sampling and closing the tanker, respectively. Personal protective equipment in the form a full face mask (EN 136) with combined filter (EN 14387) and solvex gloves is worn. This respiratory protective equipment combination gives an assigned protection factor (APF) of 10. The tanker is out of bounds and other personnel are not permitted in the area during loading operations. Furthermore, measured exposure data are available. The sample size, however, is small (n = 2) since waste transfer was performed only twice during the 2014 production campaign.

For estimation of dermal exposure RISKOFDERM 2.1 is used. Selection of the RISKOFDERM input parameters is justified as follows:

- Quality of ventilation: Normal or good ventilation applies since the activity takes place outdoors.
- Frequency of skin contact: Rare contact; dermal contact is indeed very unlikely; the outer surfaces of the equipment (loading arm, sampling rod) are not contaminated with diglyme, and operators carry out operations with greatest care
- Kind of skin contact: Light contact: According to the RISKOFDERM explanation that (potentially) contaminated surfaces are touched
- Type of product: Liquid
- Do significant amounts of aerosols occur? No: Obviously filling of solvent via a telescopic loading arm, reaching the bottom the tanker, does not generate aerosols
- Level of automation: Automated or semi-automated task: Transfer of solvent itself is controlled remotely; insertion and removal of the loading arm is done pneumatically (remote control) hence there is no dermal contact; any potential dermal contact is limited the phases of fitting a bucket below the loading arm, closing the tanker, and taking a sample using a designated sampling rod
- Application rate of product (L/min or kg/min): 200; this is the transfer rate during loading (no dermal contact); in a worst-case approach, this values is selected as a basis for estimating exposure due to potential surface contamination (if any) when closing the tanker, placing the bucket, and sampling.
- Cumulative duration of scenario per shift (min): 10; sum for removal of loading arm (including placing bucket) and sampling (5 minutes, respectively), in agreement with inhalation model (ART 1.5)

9.1.6.2 Exposure and risks for workers

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

Table 11. Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	**0.005 mg/m³** (External Tool (ART 1.5)) **Additional data not used for RCR:** < 0.11 mg/m³ (Measured HH (Measured exposure, waste transfer), values < LOQ)	RCR < 0.01
Dermal, systemic, long-term	**0.003 mg/kg bw/day** (External Tool (Riskofderm 2.1))	RCR = 0.011
Combined routes, systemic, long-term		RCR = 0.014

Remarks on exposure data

External Tool (ART 1.5)

- Inhalation, systemic, long-term:
  Scenario details
  Number of activities: 3
  Total duration (mins): 480
  Nonexposure period (mins): 350

1) Details for activity waste transfer, road tanker loading

Emission sources:	Far field
Duration (mins):	120
Far-field exposure	
Operational Conditions	
Substance emission potential	
Substance product type	Liquids
Process temperature	293 K
Vapour pressure	60 Pa
Liquid mole fraction	0.015
Activity coefficient	1
Activity emission potential	
Activity class	Falling liquids
Situation	Transfer of liquid product with flow of 100–1000 l/minute
Containment level	Handling that reduces contact between product and adjacent air.
Loading type	Submerged loading, where the liquid dispenser remains below the fluid level reducing the amount of aerosol formation
Surface contamination	
Process fully enclosed?	No
Effective housekeeping practices in place?	Yes
Dispersion	
Work area	Outdoors
Source located close to buildings?	Yes
Worker distance	> 4 m
Risk Management Measures	
Localised controls	
Primary	No localized controls (0.00 % reduction)
Secondary	No localized controls (0.00 % reduction)
Segregation	No segregation (0.00 % reduction)
Personal enclosure	Complete personal enclosure without ventilation (70.00 % reduction)

2) Details for activity remove loading arm

Emission sources:	Near field
Duration (mins):	5
Near-field exposure	
Operational Conditions	
Substance emission potential	
Substance product type	Liquids
Process temperature	293 K
Vapour pressure	60 Pa
Liquid mole fraction	0.015
Activity coefficient	1
Activity emission potential	
Activity class	Handling of contaminated objects
Situation	Activities with treated/contaminated objects (surface 0.3–1 m²)
Contamination level	Contamination > 90 % of surface
Surface contamination	
Process fully enclosed?	No
Effective housekeeping practices in place?	Yes
Dispersion	
Work area	Outdoors
Source located close to buildings?	Yes
Risk Management Measures	
Localised controls	
Primary	No localized controls (0.00 % reduction)
Secondary	No localized controls (0.00 % reduction)

3) Details for activity sampling

Emission sources:	Near field
Duration (mins):	5

Near-field exposure	
Operational Conditions	
Substance emission potential	
Substance product type	Liquids
Process temperature	293 K
Vapour pressure	60 Pa
Liquid mole fraction	0.015
Activity coefficient	1
Activity emission potential	
Activity class	Activities with relatively undisturbed surfaces (no aerosol formation)
Situation	Open surface 0.3–1 m²
Surface contamination	
Process fully enclosed?	No
Effective housekeeping practices in place?	Yes
Dispersion	
Work area	Outdoors
Source located close to buildings?	Yes
Risk Management Measures	
Localised controls	
Primary	No localized controls (0.00 % reduction)
Secondary	No localized controls (0.00 % reduction)

Predicted exposure is given as the 90th percentile full-shift exposure, for the three activities combined. The uncorrected ART estimate, not accounting for PPE, is taken forward to the risk assessment in a worst-case approach. Accordingly, PPE/RPE worn during removal of the loading arm and sampling is ignored since this would require completely separate modelling of the three activities carried out during tanker loading. Furthermore, this would complicate the comparison with measured exposures, since the measurement period covered all three activities. However, this worst-case approach is considered to be fully appropriate for risk characterisation and sufficiently protective.

Measured HH (Measured exposure, waste transfer)

- Inhalation, systemic, long-term:
  Number of measured data points: 2
  Personal exposure to diglyme was measured on two occasions while operators were conducting road tanker loading from waste tank 652.234. Sampling periods were 119 and 160 minutes. The average potential exposure for both samples was below the limit of quantitation (LOQ) of the sampling and analysis method, i.e. < 0.22 mg/m³, respectively. This value, divided by 2, to account for non-quantifiability, might be used as relevant value for risk assessment, i.e. < 0.11 mg/m³. However, a number of only two measurements is not a sufficient basis for exposure estimation (cf. ECHA guidance R.14). Therefore, the measurement data are used as supportive information to confirm low exposure as predicted by the ART model.

External Tool (Riskofderm 2.1)

- Dermal, systemic, long-term:
  RISKOFDERM calculation and subsequent modifications:
  Module "filling, mixing or loading (DEO unit 1)"
  Quality of ventilation: Normal or good ventilation
  Frequency of skin contact with the contaminant: Rare contact
  Kind of skin contact with the contaminant: Light contact
  Type of product: Liquid
  Significant amounts of aerosols or splashes generated: No
  Level of automation: Automated or semi-automated task
  Use rate of product: 200 L/min
  Resulting exposure rate hands (90th percentile): 24 mg/min
  Cumulative duration of task during a shift: 10 min
  Exposure loading per shift hands: 238 mg
  Correction for 1.5 % diglyme content in solvent waste: 3.57 mg
  Use of gloves (95 % protection); corrected exposure: 0.18 mg
  Body dose (70 kg bw): 0.0026 mg/kg bw/d

10 RISK CHARACTERISATION RELATED TO COMBINED EXPOSURE

10.1 Human health (related to combined exposure)

10.1.1 Workers

The five tasks (contributing worker scenarios) described in this CSR are performed by different operators, and each task is temporally isolated from any other task, so that combined exposure is not possible.

10.1.2 Consumers

The application for authorisation is restricted to one specific industrial use only. Consumer uses are not subject of the current CSR.

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 environment from all exposure scenarios addressed.

Table 12. Total releases to the environment per year from all life cycle stages (only one life cycle step is relevant for the current application)

Release route	Total releases per year
Water	0 kg/year
Air	0.15 kg/year
Soil	0 kg/year

Remarks:

Only one use and life cycle stage hence only one emission source is relevant for this CSR.

10.2.1.2 Regional exposure

Remarks:

In view of the strict emission control measures, releases to the environment are expected to be extremely low (see assessment of local emissions, section 9.1.1). Regional exposure can therefore be considered to be negligible.

10.2.2 Local exposure due to all wide dispersive uses

Environment

Remarks:

The current application for authorisation deals with one particular use only. The assessed use is industrial use as solvent in the manufacture of APIs one specific site. Therefore, there are no wide dispersive uses that would deserve consideration.

Man via environment

Remarks:

The current application for authorisation deals with one particular use only. The assessed use is industrial use as solvent in the manufacture of APIs at one specific site. Therefore, there are no wide dispersive uses that would deserve consideration.

10.2.3 Local exposure due to combined uses at a site

There are no combined uses at the assessed site. The current CSR is limited to industrial use as solvent in the manufacture of APIs only.

11 REFERENCES

Anonymous, 2015. Application for authorisation: DNEL setting for reprotoxic properties of diglyme. RAC/33/2015/08 rev 1, final, European Chemicals Agency, Helsinki, Finland, 05 June 2015.