CHEMICAL SAFETY REPORT

Use of bis(2-methoxyethyl) ether (diglyme) as a processing aid in the purification of 5-amino-2,4,6-triiodoisophthalic acid dichloride (EC 417-220-1; CAS 37441-29-5) by precipitation

Substance Name: bis(2-methoxyethyl) ether

Public name: Diglyme

EC Number: 203-924-4

CAS Number: 111-96-6

Registrant's Identity: Bracco Imaging s.p.a

TABLE OF CONTENTS

Part A

1. SUMMARY OF RISK MANAGEMENT MEASURES

The use of bis(2-methoxyethyl) ether (diglyme) as a processing aid in the purification of 5-amino-2,4,6-triiodoisophthalic acid dichloride (EC 417-220-1; CAS 37441-29-5) by precipitation has been assessed in part B of this chemical safety report.

Diglyme (CAS 111-96-6; EC 203-924-4) is classified as toxic for reproduction category 1B , H360FD ("May damage fertility; May damage the unborn child"). As a threshold substance, the AfA for diglyme can proceed via the adequate control route.

Bracco Imaging s.p.a. receives diglyme through the supply chain and Risk Management Measures have been communicated through the safety data sheet from supplier. However, the safety data sheet for the supplier currently lists the DNELs derived by the lead registrant during the course of the registration. The applicant is deviating from the current lead dossier in using the threshold DNEL values established in June 2015 by the ECHA Risk Assessment Committee (RAC) for the purpose of evaluation of uses subject to authorisation. The DNELs used are as follows:

- Worker (inhalation): 1.68 $mg.m^{-3}$
- Worker (dermal): 0.24 $mg.kg\ bw^{-1}.day^{-1}$
- General population (inhalation): 0.30 $mg.m^{-3}$
- General population (dermal): 0.09 $mg.kg\ bw^{-1}.day^{-1}$

Following REACH, Article 62(4)(d), the CSR supporting an AfA needs to cover only those potential risks arising from the intrinsic properties specified in Annex XIV. Accordingly, only the potential human health risks related to diglyme being classified as toxic to reproduction are considered in the current CSR.

Risk management measures are given in the summary table on pages 1 and 2 of Part B of this document.

2. DECLARATION THAT RISK MANAGEMENT MEASURES ARE IMPLEMENTED

The risk management measures mentioned in section 9 of part B are implemented by the applicant.

3. DECLARATION THAT RISK MANAGEMENT MEASURES ARE COMMUNICATED

The risk management measures mentioned in section 9 of part B are communicated to all Bracco Imaging s.p.a. employees involved in the manufacturing process described.

9. EXPOSURE ASSESSMENT (and related risk characterisation)

9.0. Introduction

Diglyme has been included in Annex XIV to Regulation (EC) No 1907/2006 ('REACH') as it is classified as toxic for reproduction 1B , H360FD ("May damage fertility; May damage the unborn child") under the CLP Regulation.

This Chemical Safety Report (CSR), and the associated worker exposure scenarios are tailored to support the Application for Authorization (AfA) to continue as a processing aid in the purification of 5-amino-2,4,6-triiodoisophthalic acid dichloride (EC 417-220-1; CAS 37441-29-5) by precipitation after the sunset date of 22 August 2017.

Diglyme is used by Bracco Imaging s.p.a as a processing aid in the purification of 5-amino-2,4,6-triiodoisophthalic acid dichloride (EC 417-220-1; CAS 37441-29-5), which is an intermediate in the multi-step synthesis of Iopamidol, an x-ray contrast imaging agent.

Diglyme is used as a co-solvent in the solubilisation of the N-sulphinyl derivative of the acid chloride followed by its subsequent hydrolysis and crystallisation to yield 5-amino-2,4,6-triiodoisophthalic acid dichloride. Diglyme is subsequently recovered by vacuum distillation and recycled. Contaminated diglyme that cannot be recycled (part of bottom fraction of the distillate, a mixture of water, diglyme and NaOH) is treated in an on-site biological waste water treatment plant.

Diglyme is consumed at an average annual rate of between 200-250 mT per annum.

As a threshold substance, the AfA for Diglyme can proceed via the adequate control route. In June 2015, The Risk Assessment Committee (RAC) published the following DNELs as non-legally binding 'reference values'. These provide applicants with a clear signal as to how RAC is likely to evaluate these elements of the risk assessment of AfA. The DNELs proposed are:

- Worker (inhalation): 1.68 $mg.m^{-3}$
- Worker (dermal): 0.24 $mg.kg\ bw^{-1}.day^{-1}$
- General population (inhalation): 0.30 $mg.m^{-3}$
- General population (dermal): 0.09 $mg.kg\ bw^{-1}.day^{-1}$

Following REACH, Article 62(4)(d), the CSR supporting an AfA needs to cover only those potential risks arising from the intrinsic properties specified in Annex XIV. Accordingly, only the potential human health risks related to diglyme being classified as toxic to reproduction are considered in the current CSR.

The dominating health effect resulting from the intrinsic hazardous properties of diglyme is damage to fertility and damage to the unborn child due to inhalation. As such only uses by workers in industrial settings are relevant and evaluation of any potential hazard to the environment is not required within the framework of this AfA. Health hazards may potentially relate to diglyme exposure of the general population via the environment, and are considered accordingly in the section *Man (via Environment)*.

This AfA does not include use of diglyme in any consumer products as diglyme is not used in any consumer products. Downstream use is not considered as Bracco Imaging s.p.a. does not supply any product containing diglyme to its customers.

9.0.1. Overview of uses and Exposure Scenarios

As described above only uses by workers in industrial settings are relevant for this CSR supporting the AfA

Tonnage information:

Assessed tonnage: [redacted] tonnes/year

CBI2

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

Table 2 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 of diglyme as a processing aid in the purification of an acid dichloride by precipitation - Use of diglyme at an industrial site (ERC 4) - Delivery and unloading of diglyme (PROC 8b) - Use of diglyme in production (PROC 1) - Recovery of diglyme (PROC 1) - Recovery of diglyme: Sampling and charging (PROC 3)	[redacted]
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-#.)			

CBI2

9.0.2. Introduction to the assessment

9.0.2.1. Environment

Evaluation of any potential hazard to the environment is not required within the framework of this AfA and has therefore not been performed in this CSR. Health hazards may potentially relate to diglyme exposure of the general population via the environment, and are considered accordingly.

Bracco Imaging s.p.a. implements the following risk management measures, to prevent or limit release of diglyme to the environment:

- **Delivery:** Diglyme is delivered to the site via a road tanker and is discharged by gravity to the underground storage tanks via flexible hose. Coupling of the hose to the connectors on the tanker is carried out manually by on-site personnel wearing respiratory protection (gas masks with charcoal filters) and protective gloves. The transfer of diglyme takes place in the open air on a hard standing area with contained drainage. A specific management procedure ('Modalità di scarico solventi e/o reagenti da auotcisterna rep. 9, May 25th 2015) controls the method by which the tanker is discharged to ensure that hoses are properly drained to the underground storage tank. Any residual diglyme from the uncoupling of the hose is rinsed with water into the contained drainage system from where it is transferred to the waste water treatment plant.

- **Synthesis and purification of 5-amino-2,4,6-triiodoisophthalic acid dichloride:** This takes place in a closed, dedicated process train, including the final isolation of the intermediate by centrifugation, under nitrogen inertion with hard piping for all inputs and outputs. The system is fully enclosed with no opportunity for worker exposure to diglyme during charging or subsequent isolation processes. Process exhaust emissions from venting processes are discharged to the vent system as described below.

- **Diglyme recovery**: diglyme is recovered, following phase separation from the mother liquor isolated during the centrifugation, by distillation under reduced pressure. All recovery operations are conducted in closed equipment with exhaust emission being vented (from process equipment and vacuum pumps) to the vent system as described below.

- **Air Emission Treatment:** process emissions from venting processes from the storage tanks and from the process train are treated by either thermal treatment or by a once through wet scrubber. Water from the wet scrubber is treated through the waste water treatment plant. Emissions of diglyme to air are very

low (see Section 9.1.1) but they have been considered in this assessment as a factor potentially contributing to diglyme exposure of humans via the environment. The scope and type of the assessment of the pathway "man via the environment" is discussed below.

- **Waste Water Treatment:** All waste water streams from the production process and solvent recovery are treated by biological treatment in the on-site WWTP. The combined final treated effluent is discharged to the surface water (River Lombra) and the waste sludge is disposed of as non-hazardous waste (via the spreading on the soil) by licenced contractors (in accordance with Italian law). Exposure of man via the environment from the potential discharge of residual diglyme in the final treated effluent is considered in Section 9.1.1.

- **Waste Treatment:** No other waste streams containing diglyme are produced by this process

Scope and type of assessment

The scope of exposure assessment and type of risk characterisation required for the environment are described in the following table.

Table 3 Type of risk characterisation required for the environment

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

Comments on assessment approach:

In accordance with REACH, Article 62(4)(d), potential risks to the environment need not be considered.

9.0.2.2. Man via environment

As discussed above humans may potentially be exposed to diglyme via the environment and the relevant potential exposure path is inhalation of emissions from the facilities to air (see also "comments on assessment approach" below) or via the food chain.

Bracco Imaging s.p.a. has evaluated the use of diglyme on-site on an annual basis and the mass balance is detailed in Table 4.

Table 4 Mass Balance

INPUT				
	Kg per batch	**Batch per day**	**Days per annum**	**mT per annum**
Amount of Diglyme used in process	[redacted]	[redacted]	[redacted]	[redacted]
Amount of Diglyme recycled	[redacted]	[redacted]	[redacted]	[redacted]
Amount of Diglyme purchased				[redacted]
Recycle rate of diglyme				8.4

CBI1

CBI2

OUTPUT			
Loss of Effluent	**Amount**	**Unit**	**Comment**
Total Flow	2,665,507	m^3/year	Measured annual total flow
Average daily flow	8,476	m^3/day	90th percentile of daily flow values
Loss of diglyme to waste water	[redacted]	mt/annum	
Default inlet concentration	93.79	mg/l	Amount purchased / total annual waste water flow
Default outlet concentration	<0.5	mg/l	Measured (< detection limit of 0.5 mg/l)
Removal efficiency	99.47	%	
Total Loss to Water	**1,332.75**	**kg/annum**	Overestimate as based on using detection limit as concentration value as default
	1.33	**mt/annum**	
Emission factor to water	[redacted]	**%**	Based on amount of diglyme used in production process in year
Loss to Air (2015 monitoring results)	**Amount**	**Unit**	**Comment**
Inlet concentration (scrubber)	6-23	mg/m^3	Measured
Outlet concentration (scrubber)	<0.4	mg/m^3	Measured but below detection limit of 0.4 mg/m^3
Flow (scrubber)	2,130	m^3/h	Measured
Mass emitted (scrubber)	7.16	kg/year	
Removal efficiency (scrubber)	95.36	%	Based on average mass removed
Inlet concentration (oxidiser)	13-15	mg/m^3	Measured
Outlet concentration (oxidiser)	<0.4	mg/m^3	Measured but below detection limit of 0.4 mg/m^3
Flow (oxidiser)	4,010	m^3/h	Measured
Mass emitted (oxidiser)	13.47	kg/year	
Removal efficiency (oxidiser)	97.13	%	Based on average mass removed
Total Loss to Air	**20.63**	**kg/year**	
Emission factor to air	[redacted]	**%**	Based on amount of diglyme used in production process in year

Monitoring results for air emissions from the scrubber and oxidiser and emissions to water are found in Annex A.

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.

Table 5 Type of risk characterisation required for man via the environment

Route of exposure and type of effects	**Type of risk characterisation**	**Hazard conclusion**
Inhalation: Systemic, long-term	Quantitative	DNEL (Derived No Effect Level) = 0.3 mg/m^3

9.0.2.3. Workers

Scope and type of assessment

Diglyme is not classified regarding acute inhalative or dermal toxicity. Thus, short-term exposure (peak exposure) has not been assessed.

The scope of exposure assessment and type of risk characterisation required for workers are described in the following table.

Table 6 Type of risk characterisation required for workers

Route	Type of effect	Type of risk characterisation	Hazard conclusion
Inhalation	Systemic, long-term	Quantitative	DNEL (Derived No Effect Level) = 1.68 mg/m³
Dermal	Systemic, long-term	Quantitative	DNEL (Derived No Effect Level) = 0.24 mg/kg bw/day

General information on risk management related to toxicological hazard:

At Bracco Imaging s.p.a. the hierarchy of control is implemented in controlling the risk associated with the use of diglyme as follows:

1) *Use of engineering controls*:
   a. Closed and dedicated process train for the manufacture of the intermediate;
   b. Recovery and re-use of diglyme in the manufacturing process;
   c. Treatment of atmospheric emissions by either thermal oxidation of wet scrubbing; and
   d. Treatment of all waste water streams by biological treatment in the WWTP;

2) *Use of administrative / procedural controls*: Bracco Imaging s.p.a. has implemented management procedures and conducted risk assessments to identify and implement proper control methodologies to minimise exposure to diglyme during the individual process operations. Bracco Imaging s.p.a are certified under ISO 14001 (Certification No. 3123), OHSAS 18001 (Certification No. 13943) as well as having an excellence certification issued by Certiquality. Certiquality is a certification body that specializes in the certification of quality, environmental, and health and safety management systems. All formulation and manufacturing procedures are documented and workers are trained in the hazards associated with the use of diglyme at elevated temperatures. Bracco performs safety training on a regular basis in line with local legal requirements and also in line with the above certifications. The total number of annual Environmental, Health and Safety (EHS) training hours given at the site is provided below.

	Hours Training Received		
	2013	2014	2015
Total EHS Training Hours	804.75	1662.0	1111.0
No. of Employees	300	300	300
Average EHS training hours per employee	2.7	5.5	3.7

An example of the training received is shown in Annex D of this document: “Estratto DVR – Chemical Risk Assessment.” This document is in Italian (as is all Bracco documentation) and states that a Bracco employee with potential exposure to this task has to complete this training every 3 years (or sooner if there has been a change in material, supply or delivery).

3) *Use of personal protective equipment (PPE)*: All site workers have to wear coveralls, safety shoes, and a dust mask. The other PPE is only required for specific tasks. The main use of diglyme at the site is in production (WCS2) and recovery (WCS3). As confirmed in each of these WCS the use of diglyme for these processes is in a closed system, PROC 1. The workers involved in these tasks do not handle diglyme, with their main tasks being that of monitoring the control panels to ensure the equipment is working as it should be and there no faults. As such there is no requirement to wear PPE such as gas masks. If and when one of the workers is required to charge NaOH to the distillation unit and / or take a sample of diglyme from the closed sampling point of the distillation unit then the full PPE is worn, as per

the hierarchy of control.

Equipment	Make Model
Gloves	MAPA Ultranitril 492[1] - this glove is used on site Ansell PVA 15-554[2] - for the unloading of diglyme from the tanker Ansell Barrier 02-100 (liner glove)[3]
Dust Mask	PF2 Draeger 1320[4]
Goggles	Peltor Visor V4D[5]
Facial Gas Mask	X-PLORE 6300 DRAGER PANORAMA NOVA RA STANDARD[6]
Multi-purpose filter	BLS mod. 425 Tipo A2B2E2K2P3 R)[7]
Safety Shoes	N/A

9.0.2.4. Consumers

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

[1] http://www.mapa-pro.net/our-gloves/protections/chemical-protection/p/g/ultranitril-492.html

[2] http://www.ansell.com/en-US/Products/All/PVA-15-554.aspx

[3] http://protective.ansell.com/en/Products/Trellchem/Gloves1/Ansell-barrier-glove/

[4] http://www.draeger.com/sites/assets/PublishingImages/Products/com_x-plore_1300/Attachments/x-plore_1300_br_9046612_en.pdf (Page 3)

[5] http://www.aearo.com/peltor.com/head_detail.cfm?prod_family=Visor%20Screens/Window&ind_prod_num=V4D001

[6] http://www.draeger.com/sites/en_aunz/Pages/Applications/Draeger-X-plore-6300.aspx

[7] http://www.blsgroup.it/filters/bls-400-series-universal-connection.html

9.1. Exposure scenario 1: Use at industrial site - Use of diglyme as a processing aid in the purification of an acid dichloride by precipitation

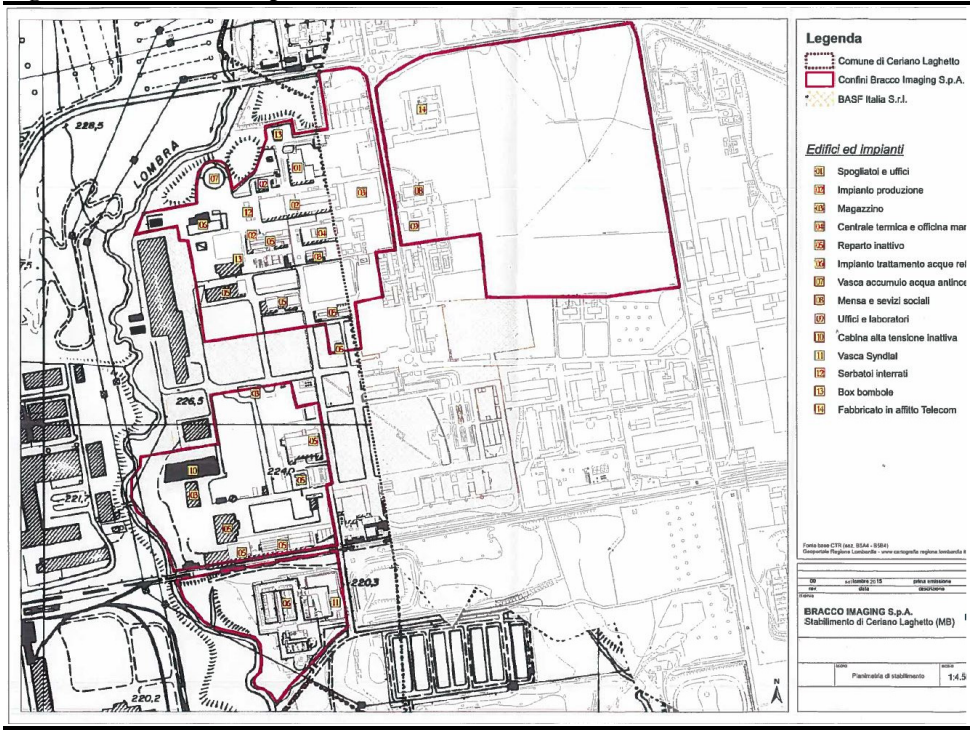
Sector of use:
SU 9, Manufacture of fine chemicals

Environment contributing scenario(s):	
Use of diglyme at an industrial site	ERC 4
Worker contributing scenario(s):	
Delivery and unloading of diglyme	PROC 8b
Use of diglyme in production	PROC 1
Recovery of diglyme:	PROC 1
Recovery of diglyme: Sampling and charging	PROC 3

Subsequent service life exposure scenario(s): Not relevant.

Figure 1 details the site plan at Bracco Imaging s.p.a..

Figure 1 Site Map



Description of the activities and technical processes covered in the exposure scenario:

Diglyme is used by Bracco Imaging s.p.a. as a processing aid in the purification of 5-amino-2,4,6-triiodoisophthalic acid dichloride (EC 417-220-1; CAS 37441-29-5) by precipitation. As discussed above, only uses by workers in industrial settings are relevant for this authorisation.

Explanation on the approach taken for the ES:

Occupational exposure estimates are based on a combination of measured and modelled data for exposure by inhalation and on modelled data for dermal exposure.

The detailed worker Exposure Scenario has been developed from the worker contributing scenarios based on information provided by the Bracco Imaging s.p.a.. This information details the conditions under which the activity was carried out as well as the duration and frequency of each task.

Operating conditions and RMMs follow the hierarchy of control outlined earlier. The workers are potentially exposed to diglyme through a combination of distinct contributing scenarios, each of which is defined in the table above.

Preventative maintenance is carried out on a regular basis to ensure the proper operation and continued levels of containment of this closed process. There are 132 documented maintenance activities that are scheduled for the pharmaceutical intermediate and diglyme recovery plant. Of these:

- 1 is carried out every 3 years, 60 minutes duration
- 100 are carried out on an annual basis and are of average duration between 30 and 60 minutes
- 24 are carried out semi-annually and are of 15-20 minutes duration
- 4 are carried out quarterly and are of 20 to 60 minutes duration
- 2 are carried out every two months and are of 60 minutes duration
- 1 is carried out weekly, of 25 minutes duration

These maintenance activities cover a wide range of activities, including control loop calibration and monitoring and control equipment calibration. All maintenance activities are carried out under a permit to work system in which the requirement for the removal and decontamination of the equipment is evaluated on a case by case basis and the appropriate risk management measures implemented to ensure minimal exposure to any chemical or physical hazards.

Repair activities are assessed on an as required basis as equipment failures occur. Bracco have a detailed understanding of equipment failures on both the pharmaceutical and solvent recovery plant and these relate primarily to hydraulic failures (pump or pipe blockages and motor failure), instrument failures (pH and actuated valve failures) and electrical failures. Each repair situation is assessed prior to work commencing and the appropriate risk management measures put in place to ensure that the repair activity is undertaken with minimal overall risk. Risk management measures will include physical isolation of the equipment, followed by drainage and decontamination if required, prior to commencement of repair work. Exposure is therefore limited in frequency and potential duration depends on the time required for the decontamination of equipment, during which time the process operators or maintenance engineers undertaking the equipment isolation will wear the protective equipment prescribed by the individual risk assessment.

Monitoring Data

Occupational Monitoring

An industrial health (IH) monitoring survey was undertaken at Bracco Imaging s.p.a. by the internal Occupational Health and Safety Department (2010-2015). Monitoring was carried out on specific tasks, namely the discharging of sodium hydroxide (NaOH) into the distillation unit and the sampling of diglyme from the distillation unit, (WCS4 in this CSR), by a qualified occupational hygienist using personal monitoring. Personal dosimeters were attached to the overalls of selected operators at chest height and air was sampled at a known rate through the charcoal absorbent for a specified period of time covering the activity. After desorption the diglyme content was determined by a gas chromatographic method (OSHA PV 2013). Results of this monitoring can be found in Table 11.

No direct dermal monitoring of the occupational exposure is possible and indirect biomonitoring is not substantiated for such low levels of exposure to diglyme. It is understood that monitoring for one of the possible metabolites of diglyme, 2-methoxyacetic acid, in urine is a potential route for demonstration of exposure to diglyme (Diethylene glycol dimethyl ether, WHO, 2002) but this has not been undertaken by the applicant. The applicant is not aware of any method of biomonitoring that has been either endorsed or recommended in preparation for the authorisation of this substance

Air Emissions Monitoring

Air emissions monitoring was undertaken at Bracco Imaging s.p.a. by Labo Consult s.r.l. (2012-2014) and by SGS Italia S.p.A (2011-2012). When measuring the concentration of diglyme emitted to the atmosphere both SGS and

Labo Consult used the method *EN 13649 (2002): Stationary source emissions – Determination of the mass concentration of individual gaseous organic compounds – Activated carbon and solvent desorption method.* According to the UK Environment Agency[8] this method was developed for monitoring individual VOC emissions from solvent using processes. It specifies procedures for the sampling, preparation and analysis. The VOCs are expressed as concentrations of individual species, averaged over a sampling period. The standard has been validated as suitable for use in the range from 0.4 mg/m^3 up to 2000 mg/m^3. The standard is based on the principles of sampling onto adsorption media followed by desorption and analysis by gas chromatography.

Waste Water Monitoring

Final treated effluent from the waste water treatment plant was performed by SGS Italia Environmental Services for a number of parameters, including diglyme concentration using the method EPA 8015C (2007). The limit of detection for this method is quoted as 5 mg/l.

Monitoring results for the above monitoring are noted in the relevant sections in the CSR and full copies of the monitoring results can be found in Annex A.

Modelling Data

Chesar2 modelling was carried out for this exposure scenario and the Environmental Contributing Scenario and Worker Contributing Scenarios listed in the Table above.

As detailed on the ECHA website *"Chesar is an application developed by ECHA to help companies to carry out their chemical safety assessments (CSAs) and to prepare their chemical safety reports (CSRs) and exposure scenarios (ESs) for communication in the supply chain. Chesar enables registrants to carry out their safety assessments in a structured, harmonised, transparent and efficient way. This includes the importing of substance-related data directly from IUCLID, describing the uses of the substance, carrying out exposure assessment including identifying conditions of safe use, related exposure estimates and demonstrating control of risks."*[9]

The model was run by Environmental Resources Management, a consultancy working with Acton for the purpose of this AoA. Chesar2 uses ECETOC TRA (version 3.1) to carry out work place assessments and EUSES 2.1.2 for Environmental assessments. The input parameters of the WCS and ECS are given in the subchapters "Conditions of Use", as per the report format generated by Chesar.

9.1.1. Environmental contributing scenario 1: Use of diglyme at an industrial site

9.1.1.1. Conditions of use

Amount used, frequency and duration of use (or from service life)
Annual use at a site: [redacted] tonnes/year (approx.)
Conditions and measures related to sewage treatment plant

• Municipal STP: No
• On-site sewage treatment plant: Yes
  ○ Details of conditions at, and emission from, on-site sewage treatment plant given in Mass Balance
  ○ Emission to receiving water: **1.33 mT / annum** (this is a conservative value as it is based on the detection limit and all monitoring of diglyme in effluent was below detection limit)
  ○ Discharge of effluent from on-site sewage treatment plant to River Lombra

CBI2

[8] https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/301194/TGN_M16_-_Monitoring_volatile_organic_compounds_in_stack_gas_emissions.pdf

[9] https://chesar.echa.europa.eu/

○ Application of the STP sludge on agricultural soil: Yes
Conditions and measures related to treatment of waste (including article waste)
• Air Emissions - treated by thermal oxidation or wet scrubbing. Results of emissions given in Annex A ○ Total emissions to air: **20.63 kg / annum** • All other solid waste removed and disposed of by licenced waste contractors
Other conditions affecting environmental exposure
Receiving surface water flow rate: >= 1.8E4 m^3/d (Chesar Model Default)

9.1.1.2. Releases

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

Table 7 Local releases to the environment

Release	Release factor estimation method	Explanation / Justification
Water	Measured release	**Local release rate:** 32 kg/day (see mass balance)
Air	Measured release (Combined scrubber and oxidisation emissions)	**Local release rate:** 0.084 kg/day (see mass balance)
Soil	ERC based	**Final release factor:** 5% (Chesar Model Default) **Local PEC**: 0.9 ng/kg

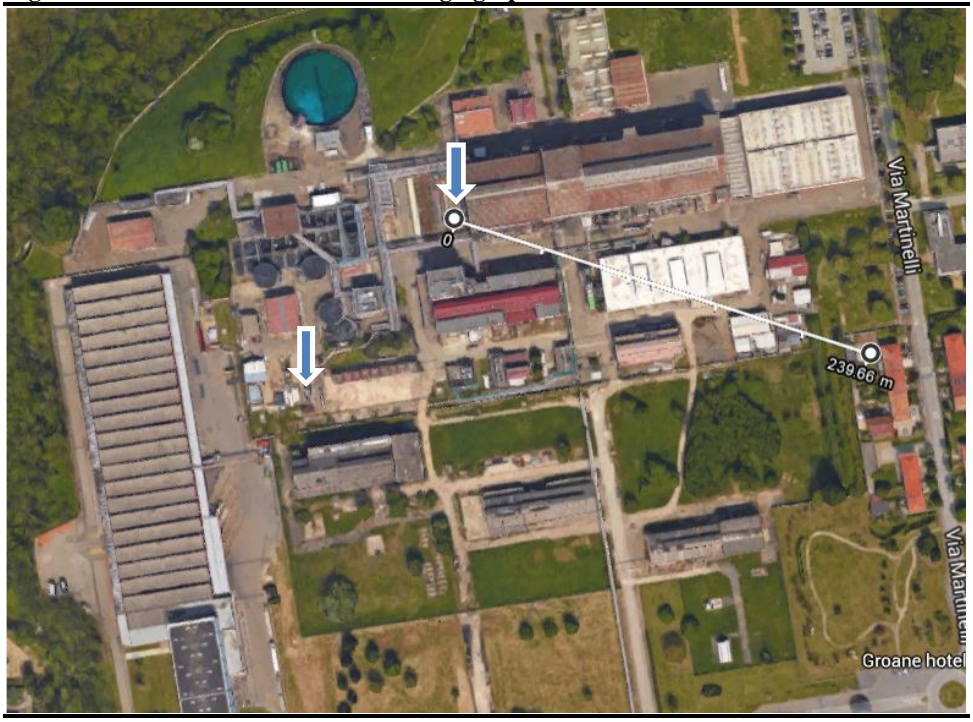
9.1.1.3. Exposure and risks for the environment and man via the environment

Using the overall release to atmosphere per day given in the table above (0.08 kg/day) Chesar modelling was carried out to estimate the local predicted environmental concentrations (local PEC). This Local PEC is compared to the RAC DNEL (General population (inhalation): 0.30 mg/m^3) and a risk characterisation ratio is calculated. The Local PEC is calculated for a point 100m from the emission point source. The nearest housing to Bracco Imaging s.p.a. is >200 m to the east of the site (see Figure 2). The location of potential exposure for man via the environment is further from the site than the distance for which the Local PEC is calculated. Table 8 reports the Local PEC and risk characterisation ratio (RCR) and shows that even using the conservative Local PEC value the RCR is < 0.01.

Table 8 Exposure concentrations and risks for the environment

Protection target	Exposure concentration	Risk characterisation
Man via environment - Inhalation	**Local PEC:** 1.922E-6 mg/m^3	RCR < 0.01

Figure 2 Location of Bracco Imaging s.p.a.



Note: Arrows indicate the emission points E1 and E4

The predicted exposure concentration in food for secondary poisoning was included in the CSR submitted by the lead registrant as part of the REACH registration dossier for diglyme (Section 9.1.2.3 in lead registrants CSR). The calculation in the registrants CSR was based on the tonnage of Diglyme used in the EU, and the values were calculated using EUSES Version 2.1 for the life-cycle step industrial use. The results are shown in the table below.

[4 "SOLVENT LARGE"] [INDUSTRIAL USE]		
CONCENTRATIONS IN FISH, PLANTS AND DRINKING WATER [4 "SOLVENT LARGE"] [INDUSTRIAL USE]		
Local concentration in wet fish	2.12E-04	[mg.kg-1]
Local concentration in root tissue of plant	6.34E-05	[mg.kg-1]
Local concentration in leaves of plant	4.28E-06	[mg.kg-1]
Local concentration in grass (wet weight)	3.78E-06	[mg.kg-1]
Fraction of total uptake by crops from pore water	0.153	[-]
Fraction of total uptake by crops from air	0.847	[-]
Fraction of total uptake by grass from pore water	0.0415	[-]
Fraction of total uptake by grass from air	0.959	[-]
Local concentration in drinking water	1.50E-04	[mg.l-1]
Annual average local PEC in air (total)	1.04E-07	[mg.m-3]
CONCENTRATIONS IN MEAT AND MILK [4 "SOLVENT LARGE"] [INDUSTRIAL USE]		
Local concentration in meat (wet weight)	6.76E-09	[mg.kg-1]
Local concentration in milk (wet weight)	6.76E-08	[mg.kg-1]
Fraction of total intake by cattle through grass	0.03	[-]
Fraction of total intake by cattle through drinking water	0.968	[-]
Fraction of total intake by cattle through air	1.50E-03	[-]
Fraction of total intake by cattle through soil	2.11E-04	[-]
DAILY HUMAN DOSES [4 "SOLVENT LARGE"] [INDUSTRIAL USE]		
Daily dose through intake of drinking water	4.28E-06	[mg.kg-1.d-1]
Fraction of total dose through intake of drinking water	0.843	[-]
Daily dose through intake of fish	3.48E-07	[mg.kg-1.d-1]
Fraction of total dose through intake of fish	0.0684	[-]

Daily dose through intake of leaf crops	7.33E-08	[mg.kg-1.d-1]
Fraction of total dose through intake of leaf crops	0.0144	[-]
Daily dose through intake of root crops	3.48E-07	[mg.kg-1.d-1]
Fraction of total dose through intake of root crops	0.0685	[-]
Daily dose through intake of meat	2.91E-11	[mg.kg-1.d-1]
Fraction of total dose through intake of meat	5.72E-06	[-]
Daily dose through intake of milk	5.42E-10	[mg.kg-1.d-1]
Fraction of total dose through intake of milk	1.07E-04	[-]
Daily dose through intake of air	2.98E-08	[mg.kg-1.d-1]
Fraction of total dose through intake of air	5.87E-03	[-]
Local total daily intake for humans	5.08E-06	[mg.kg-1.d-1]

**Diglyme has been registered in the band 100-1,000 mT per annum.*

Conclusion on risk characterisation:

The Local PEC for Man via environment (Inhalation) of **1.922 ng (diglyme)/m^3** has been calculated as the basis of the risk characterisation for this ECS. The risk characterisation ratio (RCR) for Man via Environment – Inhalation is <0.01.

The daily dose of diglyme in humans through intake of drinking water, fish, crops, meat, air and milk is very low; the Local total daily intake for humans estimated at 5.08 x10-6 mg/kg bw/day. When compared to the lowest calculated RAC DNEL (General Population (Dermal) of 0.09 mg (diglyme)/kg bw/day) the calculated RCR is <<0.1.

9.1.2. Worker contributing scenario 1: Delivery and unloading of diglyme (PROC 8b)

Diglyme is delivered to the site via a road tanker, which is parked and unloaded on a dedicated outdoor unloading area with contained drainage. The tanker is discharged by gravity to the underground stainless steel storage tank with return venting from the headspace of the underground storage to the tanker. The underground tank is contained in a secondary concrete containment sump, which is emptied under level control to the on-site biological waste water treatment plant.

Coupling of the discharge hoses to the tanker is carried out manually by on-site personnel wearing respiratory and dermal PPE (see conditions of use). At the end of the unloading operation, the residual diglyme in the discharge hose is drained to the underground tank by manual raising the hose prior to insertion of blind flanges on the tanker discharge point. This minimises discharge of any residual solvent to the contained drainage area. Any small volume of diglyme that may be spilt from the uncoupling of the hose is rinsed with water into the contained drainage where it is transferred directly to the WWTP. Figure 3 shows the area the hoses are coupled / uncoupled for the delivery of diglyme to the site.

Figure Error! No text of specified style in document.**3** **Diglyme delivery point**

Delivery of diglyme occurs approximately once a month.

Distribution of diglyme to the production plant is on demand through closed, dedicated stainless steel process lines to a dedicated stainless steel process tank using a stainless steel, magnetically coupled pump.

9.1.2.1. Conditions of use

	Method
Product (article) characteristics	
Concentration: Substance as such (100%)	TRA Workers 3.0
Amount used (or contained in articles), frequency and duration of use/exposure	
Duration of activity: < 15 minutes exposure • < 1 min coupling of the transfer hose • 1.5-2 hours transferring of diglyme to underground storage tank (no exposure) • < 1 minute uncoupling of the transfer hose • [redacted] mT diglyme delivered per annum – replacing diglyme "lost" in the synthesis route, i.e. diglyme that cannot be recovered and reused. • [redacted] deliveries per annum ○ 20 mT diglyme (approx.) per delivery • Line Operators: 1 x FTE (full time equivalent)	TRA Workers 3.0
Technical and organisational conditions and measures	
General ventilation: Outdoor Containment: • Semi-closed process with occasional controlled exposure; • Charging does not take place until the hoses are coupled to the road tanker; • Transfer from the road tanker to the underground tank is a closed system with headspace venting back to the tanker; • Training manual and risk assessments	TRA Workers 3.0
Occupational Health and Safety Management System: • Advanced • The hierarchy of control is used • Internal process documentation: ○ Document DE-B-00-0-002E06 (25/05/2015) '*Modalità di scarico*	TRA Workers 3.0

CBI2

	Method
solventi e/o reagenti da autocisterna rep. 9'. o Document DF-K-00-0-005E01 (27/04/2015) '*Analisi di operabilitàmediante metodologia hazop per l'unita serbatoi di stoccaggio in vasca interrata fabbricato 9*'.	
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Yes (a combination of LLDPE liner under chemical resistant butyl rubber glove gloves conforming to EN374 with a breakthrough time > 480 mins and with specific activity training) o Effectiveness Dermal: 95% • Respiratory protection: Dräger X-plore 6300 mask and BLS type ABEK2 filters o Effectiveness Inhalation: 95% o Assigned Protection Factor (APF): 30	TRA Workers 3.0
Other conditions affecting workers exposure	
• Place of use: Outdoor	TRA Workers 3.0
• Process temperature (for liquid): <= 40 °C (Default)	TRA Workers 3.0
• Skin surface potentially exposed: Two hands (960 cm^2)	TRA Workers 3.0

9.1.2.2. Exposure and risks for workers

ECETOC (version 3.1) modelling via Chesar was carried out to determine inhalation and dermal exposure to diglyme for this WCS. The results (and parameters of the model) are shown in Table 9.

Table 9 ECETOC Modelling Results for WCS1 (Inhalation and Dermal)

Scenario	WCS	PROC	Duration of Activity (mins)	Respiratory Protection	Dermal PPE	Calc. 8 hour inhalation TWA (mg/m^3)	Calc. 8 hour Dermal TWA (mg/kg/day)
Delivery and Unloading of Diglyme	WCS1	8b	<15	Yes	Yes	0.098	0.686

Conclusion on risk characterisation

An inhalation time weighted average exposure estimate of **0.098 mg (diglyme)/m^3** has been predicted by the ECETOC model, based on the parameters listed above and is used as the basis of the risk characterisation for this WCS. This exposure estimates has factored in Personal Protective Equipment (PPE) and Respiratory Protection Equipment (RPE).

A dermal time weighted average exposure estimate of **0.686 mg (diglyme)/kg/day** has been predicted by the ECETOC model, based on the parameters listed above and is used as the basis of the risk characterisation for this WCS. This exposure estimates has factored in Personal Protective Equipment (PPE).

9.1.3. Worker contributing scenario 2: Use of diglyme in production (PROC 1)

The steps for the production of the acid dichloride intermediate take place is a closed system and are summarised as follows:

- The synthesis takes place in a 4,000 L glass lined reaction vessel under nitrogen.
- The chlorination of starting material, 5-amino-2,4,6-triiodoisophthalic acid, using an hydrocarbon as a reaction solvent, is carried out at 65-70^{0}C using an excess of thionyl chloride as the chlorination agent.

- At the end of the chlorination reaction, excess thionyl chloride is distilled under vacuum and the mixture of crude 5-amino-2,4,6-triiodoisophthalic dichloride in the hydrocarbon is cooled.
- Diglyme is added.
- The pH of the mixture is adjusted by the addition sodium hydroxide solution.
- The precipitated 5-amino-2,4,6-triiodoisophthalic dichloride (acid dichloride) is pumped as a heterogeneous mixture to the centrifugation unit.
    - The wash water is transported via closed system to the wastewater treatment plant (WWTP).
- The centrifuge cake is rinsed with water, dried in a continuous air drier and the purified isolated intermediate is further processed.
- Annex E (*Prescrizione per la fabbricazione di:"Dicloruro dell'Acido 5-ammino-2,4,6-Triiodo-1,3 benzendicarbossilico" (Manufacture of 5-amino-2,4,6-triiodoisophthalic acid dichloride))* provides a process flow diagram for the above process. **CBI3**

The whole reaction described above takes placed in a closed, nitrogen inerted system. All vented gases, including air from the drying unit, are directed to a thermal oxidation unit for treatment. The conditions of use below state that 10 FTE operate and monitor this batch production. These 10 workers work in three shifts covering 24 hours (i.e. 3 workers per shift). Each worker will share the operational duties in this worker contributing scenario (WCS2) as well as WCS3 and WCS4. As such these 10 FTE share the overall exposure described in these scenarios

9.1.3.1. Conditions of use

	Method
Product (article) characteristics	
Concentration: Substance as such (100%)	TRA Workers 3.0
Amount used (or contained in articles), frequency and duration of use/exposure	
Duration of activity: < 8 hours • [redacted] hours per batch; [redacted] batches per day; [redacted] batches per annum • [redacted] kg diglyme per batch – hard piped from dedicated storage vessel • 10 FTE operate and monitor this batch production ○ Shift operation: 24 hours per day, 350 days per annum	TRA Workers 3.0 **CBI1** **CBI2**
Technical and organisational conditions and measures	

General ventilation:
• Basic general ventilation (1-3 air changes per hour)
Containment:
• Closed system (minimal contact during routine operations)
• No LEV operational in work area:
  ○ Effectiveness Inhalation: 0%
  ○ Effectiveness Dermal: 0%
	TRA Workers 3.0

Occupational Health and Safety Management System: • Advanced • The hierarchy of control is used • Internal training and risk assessments	TRA Workers 3.0
Conditions and measures related to personal protection, hygiene and health evaluation	

• Dermal Protection: Not required – closed reaction with no possibility of exposure
  ○ Effectiveness Dermal: 0%
• Respiratory Protection: Not required – closed reaction with no possibility of exposure
  ○ Effectiveness Inhalation: 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

	Method
• Skin surface potentially exposed: One hand face only (240 cm2)	TRA Workers 3.0

9.1.3.2. Exposure and risks for workers

ECETOC (version 3.1) modelling via Chesar was carried out to determine inhalation and dermal exposure to diglyme for this WCS. The results (and parameters of the model) are shown in Table 10.

Table 10 ECETOC Modelling Results for WCS2 (Inhalation and Dermal)

Scenario	WCS	PROC	Duration of Activity (mins)	Respiratory Protection	Dermal PPE	Calc. 8 hour inhalation TWA (mg/m^3)	Calc. 8 hour Dermal TWA (mg/kg/day)
Use of diglyme in production	WCS2	1	<480	No	No	0.056	0.034

Conclusion on risk characterisation

An inhalation time weighted average exposure estimate of **0.056 mg (diglyme)/m^3** has been predicted by the ECETOC model, based on the parameters listed above and is used as the basis of the risk characterisation for this WCS.

Although a dermal time weighted average exposure estimate has been calculated this WCS is a closed process where during normal operating conditions there is no potential for dermal exposure. As such the dermal exposure estimate in Table 10 is dismissed on this basis and not used in characterising the risk related to combined exposure (Section 10).

9.1.4. Worker contributing scenario 3: Recovery of diglyme (PROC 1)

The mother liquors arising from the separation of the crystalline product from heterogeneous reaction mixture are fed, via hard piping, to a liquid separator which gives rise to the following phases:

- Upper hydrocarbon phase, directed to hydrocarbon recovery
- Lower diglyme/water/impurity phase, directed to diglyme recovery

A diglyme/water mixture is recovered from the lower phase by reduced pressure distillation unit. This mixture is treated by the addition of solid sodium hydroxide to promote phase separation of the water and diglyme layers. The latter dehydrated diglyme phase is further purified by reduced pressure distillation to affect the recovery of pure diglyme which is recycled back into the process. Annex F (*PRESCRIZIONE PER IL RECUPERO DIGLIME (Process for the recovery of Diglyme)* provides a process flow diagram for the above process.

All waste streams from this recovery process are sent to the internal biological waste water treatment plant. Annex G is the schematic drawing of the transfer of waste water to the WWTP. **CBI3**

Whilst the recovery system is a closed, there are two potential points of exposure to diglyme, the addition of solid sodium hydroxide and the sampling of diglyme. WCS4 gives details of diglyme exposure for these potential exposure points.

9.1.4.1. Conditions of use

	Method
Product (article) characteristics	
Concentration: Substance as such (100%)	TRA Workers 3.0
Amount used (or contained in articles), frequency and duration of use/exposure	
Duration of activity: < 8 hours • [redacted] kg of diglyme recovered per batch; • [redacted] batches per year	TRA Workers 3.0

CBI1

CBI2

	Method
• Total recovered diglyme per annum: [redacted] mT o Assuming 350 days production this gives a recovery rate of between [redacted] mT per day • 10 x FTE operate and monitor this batch production o Shift operation: 24 hours per day, 350 days per annum o The same operators involved in synthesis (WCS2) also operate the recovery operation	
Technical and organisational conditions and measures	
General ventilation: • Basic general ventilation (1-3 air changes per hour) Containment: • Closed system (minimal contact during routine operations) • No LEV operational in work area: o Effectiveness Inhalation: 0% o Effectiveness Dermal: 0%	TRA Workers 3.0
Occupational Health and Safety Management System: • Advanced • The hierarchy of control is used • Internal training and risk assessments o Doc DG-B-1X-0-001E03, 'Gestione recupero solventi'. (16/04/2014)	TRA Workers 3.0
Conditions and measures related to personal protection, hygiene and health evaluation	
• Dermal Protection: Not required – closed reaction with no possibility of exposure o Effectiveness Dermal: 0% • Respiratory Protection: Not required – closed reaction with no possibility of exposure o Effectiveness Inhalation: 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 cm^2)	TRA Workers 3.0

9.1.4.2. Exposure and risks for workers

ECETOC (version 3.1) modelling via Chesar was carried out to determine inhalation and dermal exposure to diglyme for this WCS. The results (and parameters of the model) are shown in Table 11.

Table 11 ECETOC Modelling Results for WCS3 (Inhalation and Dermal)

Scenario	WCS	PROC	Duration of Activity (mins)	Respiratory Protection	Dermal PPE	Calc. 8 hour inhalation TWA (mg/m^3)	Calc. 8 hour Dermal TWA (mg/kg/day)
Recovery of diglyme	WCS3	1	<480	No	No	0.056	0.034

Conclusion on risk characterisation

An inhalation time weighted average exposure estimate of **0.056 mg (diglyme)/m^3** has been predicted by the ECETOC model, based on the parameters listed above and is used as the basis of the risk characterisation for this WCS.

Although a dermal time weighted average exposure estimate has been calculated this WCS is a closed process where during normal operating conditions there is no potential for dermal exposure. As such the dermal exposure

estimate in Table 11 is dismissed on this basis and not used in characterising the risk related to combined exposure (Section 10).

9.1.5. Worker contributing scenario 4: Recovery of diglyme: Sampling and charging (PROC 3)

Whilst the recovery system is a closed, there are two potential points of exposure to diglyme which has been subject to occupational exposure monitoring:

- Addition of solid sodium hydroxide to the distillation unit. This occurs through a contained, extracted charging booth (see Figure 4).
- Figure 5 shows the charging of NaOH in diagram form.
    - The pink / purple in Figure 5 represent the flexible glove box with the dark purple circles representing the gloves.
    - The bags of NaOH are brought into the glove box a spring loaded door (green box to the right of the glove box)
    - At the base of the glove box is a valve, the valve is opened to the distillation unit to charge the NaOH. At all times outside of discharging NaOH the valve is closed
    - To the right of the glove box is where all waste NaOH bags are stored
    - The blue box at the top of the glove box is an valve to the air emission ducting
    - As stated earlier in the CSR all atmospheric emissions are treated by either thermal oxidation of wet scrubbing
- Contained sampling points for diglyme, one prior to distillation and one after distillation. The construction of the sampling system is such that there are no spillages and a minimum of fugitive release of vapour (see Figure 6).

Figure 4 Enclosed Sodium Hydroxide charging booth

Figure Error! No text of specified style in document.**5** **Diagram of NaOH charging booth**

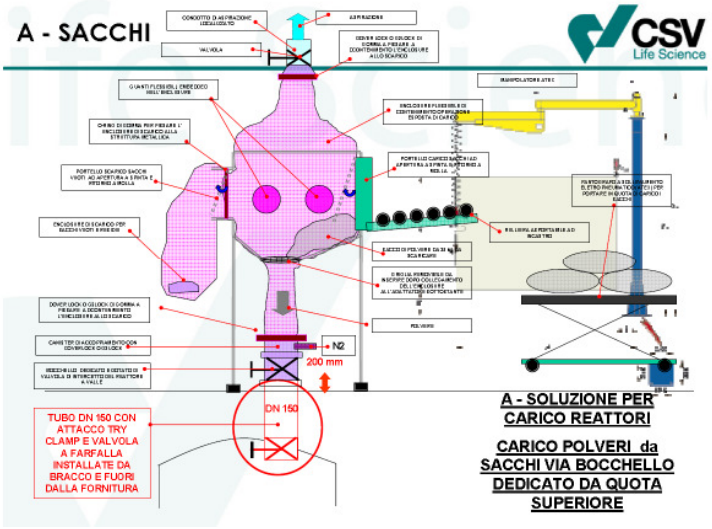


Figure 6 **Closed sampling loop**

9.1.5.1. Conditions of use

	Method
Product (article) characteristics	
Concentration: Substance as such (100%)	TRA Workers 3.0
Amount used (or contained in articles), frequency and duration of use/exposure	
Duration of activity: < 1 hour • < 5 min charging of sodium hydroxide per batch	TRA Workers 3.0

	Method

• < 1 min for each sample collection; 2 samples per batch
• [redacted] batches per year; Approx. [redacted] batches per day
• 10 x FTE operate and monitor this batch production
  o Shift operation: 24 hours per day, 350 days per annum
  o The same operators involved in synthesis (WCS2) also operate the recovery operation (WCS3 and WCS4)	

Technical and organisational conditions and measures	

General ventilation:
• Basic general ventilation (1-3 air changes per hour)
Containment:
• Closed system (minimal contact during routine operations)
• No LEV operational in work area:
  o Effectiveness Inhalation: 90%
  o Effectiveness Dermal: 90%
  o Charging of sodium hydroxide is automated process through an enclosed charging booth (glovebox – Ultranitril 492). There is no dermal contact with diglyme when charging sodium hydroxide.
	TRA Workers 3.0

Occupational Health and Safety Management System: • Advanced • The hierarchy of control is used • Internal training and risk assessments o Doc DG-B-1X-0-001E03, 'Gestione recupero solventi'. (16/04/2014)	TRA Workers 3.0
Conditions and measures related to personal protection, hygiene and health evaluation	

• Charging sodium hydroxide Dermal Protection: Yes (Ultranitril 492 conforming to EN374 with a breakthrough time)
  o Effectiveness Dermal: 95%
• Sampling Dermal Protection: Yes (chemical resistant butyl rubber glove gloves conforming to EN374 with a breakthrough time > 240 mins and with specific activity training)
  o Effectiveness Dermal: 95%
• Respiratory protection: Dräger X-plore 6300 mask and BLS type ABEK2 filters
  o Effectiveness Inhalation: 95%
  o Assigned Protection Factor (APF): 30
	TRA Workers 3.0

Other conditions affecting workers exposure	
• Skin surface potentially exposed: One hand face only (240 cm^2)	TRA Workers 3.0

CBI1

9.1.5.2. Exposure and risks for workers

Table 12 details the inhalation monitoring results obtained for this WCS.

Table 12 Monitoring Results for WCS4

Location	Duration (minutes)	Diglyme Measured Conc. (mg/m^3)					
		2010	2011	2012	2013	2014	2015
Charging NaOH to R509	30	0.023	<0.02	<0.02	0.13	<0.02	0.2
Sampling recovered diglyme	5	<0.02	<0.02	<0.02	<0.02	<0.02	SD

SD = sampling discontinued due to consecutive low monitored values
Detection limit: 0.02 mg/m^3

ECETOC (version 3.1) modelling via Chesar was carried out to determine dermal exposure to diglyme for this WCS. The results (and parameters of the model) are shown in Table 13.

Table 13 ECETOC Modelling Results for WCS4

Scenario	WCS	PROC	Duration of Activity (mins)	Respiratory Protection	Dermal PPE	Calc. 8 hour inhalation TWA (mg/m^3)	Calc. 8 hour TWA (mg/kg/day)
Recovery of diglyme: Sampling and Charging	WCS4	8b	<60	95%	95%	0.017	0.003

Conclusion on risk characterisation

The 90th percentile inhalation exposure estimate of **0.165 mg (diglyme)/m^3** is used as the basis of the risk characterisation for this WCS. This exposure estimate has been derived from measured data, using the value of 0.02 for any measurements below the limit of detection, and has factored in Personal Protective Equipment (PPE) and Respiratory Protection Equipment (RPE).

A time weighted average dermal exposure estimate of **0.003 mg (diglyme)/kg/day** has been predicted by the ECETOC model, based on the parameters listed above, and is used as the basis of the risk characterisation for this WCS.

10. RISK CHARACTERISATION RELATED TO COMBINED EXPOSURE

The risk characterisation of worker exposure to diglyme has been conducted based on the DNELs in Table 14.

Table 14 DNELs for Workers and General Population

	Long-term – systemic effects			
	Workers		General Population	
	Dermal (mg/kg bw /day)	Inhalation (mg/m^3)	Dermal (mg/kg_{bw}/day)	Inhalation (mg/m^3)
RAC DNEL	0.24	1.68	0.09	0.30

n.a. = not available

10.1. Human health

10.1.1. Workers

The worker contributing scenarios at Bracco Imaging s.p.a., outlined in Section 9, are carried out in combination by different members of the workforce. Two specific categories of worker exposure at Bracco Imaging s.p.a. have been identified as follows:

- **Production Worker 1 (PW1)**: responsible for unloading diglyme from the road tanker into the underground storage tank (WCS1); all other work carried out by PW1 has no exposure to diglyme.
- **Production Worker 2 (PW2)**: Use of diglyme in production (WCS2) and diglyme recovery (WCS3). Although diglyme recovery is a waste operation and therefore exempt for authorisation because it is so intimately integrated with the overall production process and operated at significant scale, the risk assessment includes this recovery step. The activity is shared by 10 workers at Bracco Imaging s.p.a..

Further modification of the risk assessment on the discontinuous nature of the worker activities

Table 15 details the time, on average, each production worker spends at each WCS per day and per week, and the measured exposure concentrations for each task, and modelled time weighted average exposure concentrations for inhalation and dermal exposure for each WCS identified in Chapter 9.

Due to the frequency of the work carried out by PW2, the same task on a daily basis over the 5 day week, the 8 hour TWA shown in Table 15 has been used. This 8 hour TWA is then compared to the RAC derived DNEL to determine the RCR for both inhalation and dermal exposure to diglyme. It is assumed that each of the 10 workers will be exposed to the same concentration of diglyme.

However, as the work tasks associated with PW1 do not take place on a daily basis, and as the health impact of Diglyme is a long-term reproductive effect, it is considered more appropriate to calculate the RCR for PW1 on the basis of a weekly (5 day) time weighted average. This weekly TWA is then compared to the RAC derived DNEL to determine the RCR for both inhalation and dermal exposure to diglyme. The equations used to calculate the Weekly TWA and RCR are shown below.

Weekly TWA= [(Exposure Conc. 1 x Exposure Duration 1) + (Exposure Conc. n x Exposure Duration n)] / 40

RCR = Exposure Result (Weekly TWA) / DNEL

Further modification of the risk assessment based on a qualitative assessment of dermal exposure

A further qualitative assessment of the dermal exposure pattern in relation to the protection factors afforded by the

gloves used has been undertaken for the tanker unloading activity (WCS 1). The full details of this quantitative assessment can be found in Annex B. The applicant concludes that due to the extended breakthrough times (>480 mins) of the protective dermal materials used, the actual pattern of exposure, and the extent of potential contamination by each of the work activities, there is negligible dermal exposure to diglyme at the site.

As such the dermal RCR in Table 15 derived from the ECETOC modelled dermal exposure value is further modified by a factor of 10 to account for this pattern of use on the basis of the qualitative assessment; this calculation is detailed under the row 'RCR revised' in Table 15. As the dermal PPE will effectively prevent any worker dermal exposure to diglyme, this reduction factor of 10 is still considered conservative.

Table 15 Risk Characterisation per WCS

		WCS1	WCS2^	WCS4
PW1	Hours per day	0.25		
	No. of days per week	1		
	Hours per week	0.25		
PW2	Hours per day		7	1
	No. of days per week		5	5
	Hours per week		35	5
INHALATION				
Measured Diglyme Conc. (mg/m^3)				0.165
8 hour TWA (mg/m^3)		0.098*	0.056*	0.021
Daily RCR		0.058	0.033	0.013
Weekly TWA (mg/m^3)		0.020	N/A	N/A
Weekly RCR		0.012	0.033	0.012
DERMAL				
8 hour TWA (mg/kg/day)*		0.686	N/A	0.003
Daily RCR		2.86	N/A	0.01
Daily (RCR (revised)		0.29	N/A	N/A
Weekly TWA (mg/kg/day)		0.137	N/A	N/A
RCR		0.57	0.0	0.01
RCR (Revised)		0.06	N/A	N/A

* Calculated via Chesar model

^ WCS2 is used to represent the diglyme exposure for both WCS2 and WCS3. The modelled exposure estimates for WCS2 and WCS3 are the same and PW2 would split their time between the two tasks. The hours estimated per day equate to the total time the worker would be exposed to WCS2 and WCS3.

Inhalation Exposure

Table 16 details the combined inhalation RCR for the two production workers at Bracco Imaging s.p.a.. The combined RCR is achieved by adding together the RCRs for the relevant WCS for each PW.

Table 16 RCR (Inhalation) for Production Workers at Bracco Imaging s.p.a.

Identifier	RCR (weekly): Long term (Inhalation) RAC DNEL	RCR (daily): Long term (Inhalation) RAC DNEL
PW1	0.012	0.058
PW2	0.046	0.046

Dermal Exposure

Table 17 details the dermal RCR for the two production workers at Bracco Imaging s.p.a.. The combined RCR is achieved by adding together the RCR for the relevant WCS for each PW. For PW1 the RCR (revised) is used on the basis that the ECETOC TRA3 overestimates predicted exposure and can be modified based on supporting analysis provided in detail in Annex B.

Table 17 RCR (Inhalation) for Production Workers at Bracco Imaging s.p.a.

Identifier	RCR (weekly): Long term (Dermal) RAC DNEL	RCR (daily): Long term (Dermal) RAC DNEL
PW1	0.06	0.29
PW2	0.01	0.01

Overall Exposure (Combined for all relevant emissions / release sources)

Workers are exposed to diglyme via inhalation and dermal routes of exposure. Route-specific exposure specifically contributes to the total internal body burden. Thus, concurrent exposure via various routes of exposure needs to be accounted for when characterising overall systemic health risks.

Assuming an identical toxicological profile for the various routes of exposure the overall risk is calculated according to the following formula:

RCR (for simultaneous exposure via three routes) = RCR (oral) + RCR (dermal) + RCR (inhalation)

Table 18 summarises the combined RCR for Dermal and Inhalation exposure at Bracco Imaging s.p.a.

Table 18 Combined RCR (Bracco Imaging s.p.a.)

Scenario	Combined Weekly RCR (Inhalation and Dermal)	Combined Daily RCR (Inhalation and Dermal)
PW1	0.072	0.344
PW2	0.056	0.058

The combined RCR for all PW are < 1, demonstrating that the use of diglyme is under adequate control in the current uses on site.

10.1.2. Consumer

Not relevant as there is no consumer use.

10.2. Environment (combined for all emission sources)

10.2.1. All uses (regional scale)

Not relevant as all uses at local scale.

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

Not relevant as there are no combined uses at a site.