9. EXPOSURE ASSESSMENT (and related risk characterisation)

9.0. Introduction

9.0.1. Overview of uses and exposure scenarios

The use of diglyme as a process solvent takes place at one particular Merck production site in Darmstadt (Germany). Diglyme is used in different sequenced manufacturing steps in the synthesis of Kryptofix® intermediates. 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 AoA describes the complexity of the manufacturing process of Kryptofix® for which diglyme is used as a solvent. The synthesis depends on a variety of parameters. The handling and operation of this process needs very experienced, usually senior, staff. Replacing diglyme by another solvent needs to be considered carefully in order to maintain the high quality and purity of Kryptofix®, which to date only Merck and a few competitors with their specific process and know how can provide. The quality aspect of the Kryptofix® synthesis is important regarding the highly specialised uses of the fine chemical.

The synthesis is conducted in an industrial reaction facility, with fully implemented and controlled safety measures. There is no eventuality for exposure of workers and minor for the release into the environment. After the synthesis, the precipitated reaction product is transferred into a centrifuge via fixed piping and a flexible hose.

Opportunities for exposure are, however, given during the following steps that require manual intervention:

- WCS 1 (Diglyme charging): The solvent is transferred from transport drums into the closed system (head tank). A small opening (diameter ca. 5 cm) in the barrel, where a suction lance with ca. 3 cm diameter is inserted, is the only source which could contribute to an exposure.
- WCS 2 (Addition of reaction partners): Addition of the reaction partners to the reaction chamber. This step includes opening of different orifices with diameters of 25 cm, 5 cm and 3 cm for a short time of approximately 2–5 minutes.
- WCS 3 (Transfer of diglyme from 200 L barrel into 30 L barrel). Diglyme is transferred into a barrel with 30 L volume by a manual pump and a suction lance, and afterwards water is added. During this step, which takes approximately 5 minutes, the worker remains next to the barrel.
- WCS 4 ([redacted] (Reaction Step)): The [redacted] (reaction step) by adding the water/diglyme mixture using a semi-automatic pump to the reaction chamber.
- WCS 5 (Centrifugation): The reaction mixture is transferred to the centrifuge via permanently installed airtight connections and a flexible hose. The worker operates only valves to start and stop the process. During the centrifugation process the solvent collecting barrels are exchanged four times by the operating worker.
- WCS 6 (Emptying the centrifuge): Removing the filtration cake is performed manually with a paddle. The filtration cake is transferred to the drying oven.
- WCS 7 (Distribution of wet crystals in the drying oven): The wet crystals are spread on stainless steel plates in the oven for evaporation of remaining solvent.

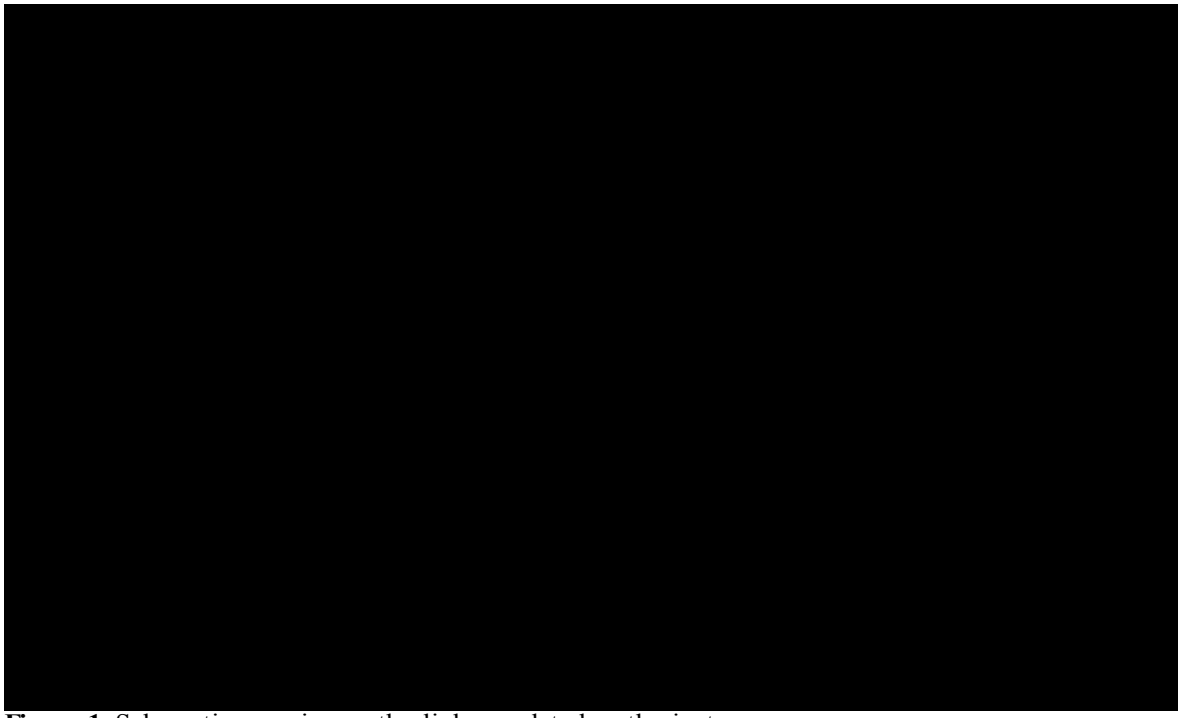

Figure 1: Schematic overview on the diglyme related synthesis steps

Improvement of the occupational safety for the manufacturing process

Merck is globally active in the chemical and pharmaceutical industry and accordingly involved in manifold projects in order to keep its processes and technologies up to date. Internal processes and Standard Operating Procedures (SOPs) ensure a regular review of the chemicals used and seek for potential alternatives and process optimisation. In addition, during new product development the avoidance of unnecessarily hazardous substances is addressed and potential alternatives are investigated if possible. In cases where the handling of hazardous substances cannot be avoided, as in the Kryptofix® synthesis, Merck continuously performs efforts to minimize contact of workers to the substances by optimizing process parameters. This includes the replacement of fittings, pumps, lances and piping equipment by airtight systems. Section 4.1.2 of the AoA document provides additional insights into the continuous development process of chemicals and products by Merck.

Personal protective equipment

Workers wear personal protective equipment (PPE) during all steps of handling and processing diglyme. PPE includes a full face mask with a composite filter (Auer 89 ABEK 2 HG/St), Nomex clothing and gloves, as illustrated in Figure 1. The full face mask is worn during any activities involving potential for exposure, primarily due to formation of [redacted] (Borane Species) as a by-product of synthesis. [redacted] (Borane Species) is a gas that is extremely toxic upon inhalation. Occupational exposure limits, where available, consequentially are very low, e.g. the Swiss MAK (maximum workplace concentration) for [redacted] (Borane Species) is 0.1 ppm[1], whereas there is currently no German MAK or other OEL value or European DNEL for this substance. The Swiss MAK value is more than a factor of 15 lower than the official long-term DNEL for diglyme. The specified filter is effective against both substances, [redacted] (Borane Species) and diglyme. Therefore, adequate protection against the (less toxic) diglyme is ensured. During the final production steps, i.e. WCS 6 and 7, the worker wears additional protective clothing, a disposable Tychem F (DuPont®) suit (see Figure 2).

[1] https://extra.suva.ch/suva/b2c/download.do?doctype=pdf&docid=00000000000004489&file=1903_D.pdf

Figure 2: PPE used for diglyme containing production steps of Kryptofix®

Maintenance of protective equipment:

Respirator mask:

The maintenance of the full face mask is subject to the specifications of the "PSA-Benutzungsverordnung (PSA-BV)" (PPE use ordinance). The PSA-BV represents a German ordinance for implementing Directive 89/656/EEC concerning occupational health and safety. The ordinance governs the provision of personal protective equipment (PPE) by the employer and its use by employees (§ 1).

§ 2 describes the basic specifications, which the employer needs to consider for the purchase, maintenance, storage and repairs. § 3 contains hints for the briefing of employees regarding the use of PPE.

The deployed full face masks are in compliance with DIN EN 136 (respiratory protective devices; full face masks; specifications; control). The relevant technical guideline concerning choice, suitability, control periods, and trainings is the DGUV rule 112-19. Besides manufacturers' instructions the control is described in the DGUV information 205-013.

Respirator masks and filters are, according to an internal SOP, collected after each shift, cleaned, fumigated, and controlled for impermeability. Trainings of employees according to the PPE use ordinance (PSA-BV) are documented in a Merck internal system.

Gloves:

Due to a penetration time of > 480 minutes gloves are replaced after each shift (in which diglyme is used). This is documented in the plant regulations.

Emergency procedures:

In case of an accident during the Kryptofix production the plant fire brigade disposes of all chemicals according to an emergency plan. For work accidents associated with diglyme like, e.g. an overturned barrel, the appropriate actions are given in the operating instructions.

Local exhaust ventilation:

All exhaust equipment was tested for performance in 2015. The measured values were between 56 and 240 m³/h, depending on the number of parallel opened air exhaust streams and the particular exhaust location. The lower value given in this CSR is considered to be a worst-case as it was the lowest measured value conducted for two different air exhaust streams.

Technical protective conditions

Air is exhausted by local exhaust ventilation (movable capturing hood) with 56 – 240 m³/h air flow via a flexible hose system that is connected with the K3 air washing system. The mobile capture device is used if containers or holes like the manhole are opened for a short period.

The air exchange rate for the production hall is 4.8 room volumes/h. The room volume is 427 m³. In the centrifugation room the air exchange rate is 3.0 room volumes/h. For all calculations below, the lowest value of 3.0 has been taken. Air exchange rates have been measured by Merck in the course of the preparation of this AfA.

Preventative maintenance

The entire equipment is maintained 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 independently from production campaigns on cleaned 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 MPs 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 the charging and production the equipment is subjected to a pressure and integrity test to ensure leak-tightness of the system. Charging and production must not start without the integrity test being passed.

Exposure measurements

Merck performed efforts during the last months to accompany synthesis campaigns by exposure measurements for the purpose of this AfA. The number of measurements are too low statistically robust exposure calculation in accordance with REACH guidelines. However, the measurements can be seen as supportive information for the purpose of this AfA. The measurements are described in detail in Section 10.1.1, since measurement periods often cover more than one WCS, thus representing combined exposure. The supportive measurements confirm the modelled exposure data and show that the adequate control is ensured for every single WCS and for combined exposures.

Brief overview of worker contributing scenarios

The whole occupational exposure scenario for the Kryptofix® process can be broken down into the following contributing scenarios (including those with no eventuality for exposure, and those with potential for exposure). It is important to note that the process runs over two consecutive days. Activities described in WCS 1–3 are performed on day 1, the remainder (WCS 4–7) on day 2. Accordingly combined exposure across several activities needs to be considered on day 1 and 2 separately (cf. chapter 10 of this CSR).

WCS 1: Diglyme charging

As initial step diglyme is charged from a 200 L barrel into an intermediate tank and afterwards into the reaction chamber by vacuum. For that purpose, a 200 L drum is placed next to the reactor and opened manually (diameter of the bung hole ca. 5 cm). A suction lance, which is connected to the intermediate tank of the reactor via a flexible hose, is inserted into the bung hole. The connection of the flexible hose to the reactor is airtight, while the lance (diameter ca. 3 cm) is placed into the open bung hole of the 200 L barrel. After opening a valve, diglyme is charged by vaccume into the reactor. After completion of the transfer to the reactor, any residual diglyme is allowed to drip from the lance into the barrel. The lance is removed, placed into the LEV and allowed to dry by the exhaust air stream. A further movable capturing hood is operated continuously during the entire charging step in close proximity to the open bung hole of the barrel. Workers wear PPE as described above during the entire operation. Figure 3 shows the bung hole with the inserted lance, and the mobile LEV system (left).

Figure 3: Charging of diglyme from a 200 L barrel into the reaction chamber via a lance.

WCS 2: Addition of reaction partners

The cryptand precursor is manually added to the synthesis reactor via the manhole (diameter = 25 cm). The task is estimated to take maximally 5 minutes. Furthermore, the second reaction partner, [redacted] (Hydride Species), is added to the reactor via the small volume opening. The overall duration of this activity (addition of reaction partners to the reactor already containing diglyme) is 20 min at maximum. LEV in the form of a movable capturing hood (flow rate was measured to be between 56 and 240 m³/h, in dependence of the settings of the multi-use facility, with 56 m³/h as lowest value) is placed in close proximity to the manhole, from which diglyme vapours may be emitted.

The following activity does not involve any handling of or exposure to diglyme, but is described under current WCS for the sake of completeness and to enable complete understanding of the process:

A complex of [redacted] (Boron Compound) and tetrahydrofurane (THF) is weighed and transferred into a barrel via a manual pump (no diglyme involved). The worker connects the barrel to the hose/pump system and initiates the dosage to the reactor by starting the dosage pump. The hose is connected to the reactor airtight; whereas the bung hole of the barrel (diameter ca. 5 cm) is covered by a cap which is not perfectly airtight but designed for restricting diffusion of vapours through this small orifice. Therefore LEV (movable capturing hood) is placed in close proximity to the bung hole.

Accordingly, exposure estimation takes only into account the phases of adding solid reaction partners via the manhole and/or small volume opening. Preparation and charging of the [redacted] (Boron Compound)/THF complex can be ignored since not contributing to diglyme exposure.

Process synthesis itself takes place in a closed reactor (see WCS 4 below). The operator does not get in direct contact with diglyme during the process synthesis tasks. The reaction partners added to the reaction chamber during this step are free from diglyme.

WCS 3: Preparation of the [redacted] (reaction mixture)

Diglyme is transferred from a 200 L barrel into a 30 L barrel using a manual pump: The bung hole of the 200 L barrel is opened and a lance equipped with gas-tight connection is inserted. This step takes only a few seconds and is performed under LEV (movable capturing hood). The opposite end of the tube, still free from diglyme, is placed into the 30 L barrel via a bung hole (diameter ca. 5 cm) which is not air tight. Diglyme is transferred via a manual pump from the larger into the smaller barrel. Afterwards water is added from the internal demineralized (VE) water network. The whole process takes 2–3 minutes; a maximum of 5 minutes are assumed for exposure estimation as a worst-case.

The worker stays next to the barrels for operating the pump until the specified amount of liquid is transferred. After completion of the diglyme transfer, the lance is removed from the bung hole and placed into the LEV to evaporate remaining diglyme. During the whole activity the worker wears PPE as described above. Figure 4 shows the 200 L and 30 L drums and the manual pump which is used for diglyme transfer between barrels.

Figure 4: Transfer from 200 L barrel to 30 L barrel for the [redacted] (reaction mixture) (diglyme and water).

WCS 4: [redacted] (reaction) of the reaction mixture

The water/diglyme mixture (50/50, w/w), see WCS 3, is added to the reaction chamber: The worker connects the 30 L barrel to the hose/pump system that was already used for [redacted] (Boron Compound)/THF complex charging (see WCS 2) and initiates the dosage to the reactor by starting the dosage pump. The worker monitors the [redacted] (reaction) permanently and is physically present in the room for approximately 1 hour. The hose is connected to the reactor airtight, whereas the bung hole of the barrel (diameter ca. 5 cm) is covered by a cap which is not perfectly airtight but designed for restricting diffusion of vapours through this small orifice. Therefore, LEV (movable capturing hood) is placed in close proximity to the bung hole. After the reaction is complete, the

tubes and lances are removed and dried by air stream in a LEV system. During these steps the worker wears the aforementioned PPE. Figure 5 illustrates the design of the connections between barrel, hose and reaction vessel.

Figure 5: Dosing of the [redacted] (reaction mixture) into the reaction chamber by a semi-automatic pump.

WCS 5: Transfer of product suspension to centrifuge and centrifugation

WCS 5 encompasses two steps: Transfer of the reaction suspension via permanently installed, airtight connected piping and partly via a flexible, but airtight hose and, secondly, centrifugation of the reaction mixture.

In the first step, the [redacted] and precipitated reaction mixture is transferred from the reaction chamber into the centrifuge. This process is performed using gravity, and assisted by pressurised nitrogen (0.3 bar), transferring the reaction mixture via a fixed and airtight piping from the reaction chamber to the centrifuge. There is no exposure potential for this completely closed process.

The second step comprises the centrifugation of the reaction mixture. The equipment used is a link-suspended centrifuge with top discharge. This type of centrifuge is airtight during operation hence the operator does not get in direct contact with diglyme during centrifugation. The centrifuge is connected to the air exhaust system which is connected to the described exhaust air washing system (wet scrubber).

However, the filtrate (diglyme/water mixture) is transferred into 200 L barrels using a pump and a filling lance connected airtight to the bung hole of these barrels. The filtrate resulting from one production batch typically corresponds to the volume of 4 barrels. Accordingly, the worker has to manually connect the hose during the changing of the barrels, taking maximally 2 minutes per barrel. The whole centrifugation task takes about 3 hours, during which the worker stays in the centrifugation room monitoring the process. After finishing the centrifugation process and before opening the centrifuge, the centrifugation cake is washed twice with water, before the centrifuge is opened. Dermal exposure is very unlikely and only possible during exchange of the barrels.

During this step the worker wears the aforementioned PPE. LEV is an integral part of the centrifuge. Furthermore, LEV in the form of a movable capturing hood is placed in close proximity of the bung hole of the barrel.

Figure 6: Airtight connections between the 200 L barrel and the centrifuge

WCS 6: Emptying of centrifuge

After the centrifugation process is finished the closed centrifuge is automatically washed with water before opening. Accordingly, no exposure can be expected during this step. Afterwards, the centrifugation cake is manually transferred into a drum by a worker, for subsequent transfer to the drying oven (see WCS 7). According to internal measurements, the wet crystals contain ca. 0.3 % diglyme. Emptying of the centrifuge takes approximately 10 minutes and the distance of the worker to the emission source can be characterised as near-field exposure.

WCS 7: Distribution of wet crystals in the drying oven

The final step includes transfer and spreading of the precipitate on metal plates which are placed into a drying oven. This activity inevitably entails near field exposure of the worker, who always wears PPE. The oven is connected to a separate exhaust air stream and no exposure can be expected after its doors are closed. The crystals contain approximately 0.3 % diglyme. Spreading of the wet crystals lasts approximately 5 minutes. The drying step is automated, with no worker being involved.

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

Table 6: 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 - Solvent for cryptand manufacturing: - Solvent for Kryptofix synthesis (ERC 4) - Diglyme charging (PROC 8b) - Addition of reaction partners (PROC 4) - Preparation of [redacted] (reaction mixture) (PROC 8b) - [redacted] (reaction step) in vessel (PROC 8b) - Transfer to centrifuge and centrifugation (PROC 8b) - Emptying of centrifuge (PROC 4) - Distribution of wet crystals in the drying oven (PROC 4)	[redacted]
Industrial end use at site: IW-#			

9.0.2. Introduction to the assessment

Diglyme has been included into Annex XIV of the REACH Regulation 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 a solvent in the manufacture of cryptands. The solvent diglyme does not end up in the final product. 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 also potentially arise due to exposure via the environment (vapour, via the food chain).

9.0.2.1. Environment

Scope and type of assessment

In view of the risk management measures in place at the applicant's production facility (collection of all solvent waste and disposal as hazardous waste by a licenced contractor – also see below) emissions of diglyme to the aquatic environment are effectively minimised. The only release pathway to the aqueous environment is wastewater from the scrubbers (central K3 scrubber receiving exhaust air from LEVs, and K2 scrubber receiving off-air from the reactor). Release rates, including justifications, are specified in the environmental contributing scenario (see section 9.1.1).

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 opportunities for release to ambient air and consequently to the environment are identified at charging of diglyme into the closed system, solvent transfer, and transfer of the filtrate from the centrifuge to the waste barrels.

In conclusion, emissions resulting from the use of diglyme as process solvent 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 7: 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 potential 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 elaborated in section 9.1.1 below, 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: The release pattern is intermittent since the interval between two successive charging events will vary between 2 days and several months, and the frequency is 20 times per year at maximum.

Airborne concentrations (PEC_{local} in a 100 m diameter around the emission source) and PEC regional are estimated using EUSES 2.1.2.

Table 8: 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 rev1)
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 the 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

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

Table 9: Type of risk characterisation required for workers

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

General information on risk management related to toxicological hazard:

Exposure of workers handling diglyme in the course of the cryptand manufacturing process is restricted to a low level:

Diglyme containing containers are only opened and closed for insertion of suction lances or similar tubes. The workers wear PPE at all stages of the process. Details on the technical procedures and safety measures are described in section 9.0.1 above. A summary of the risk management measures related to the toxicological hazard is given as follows:

- Diglyme charging from 200 L barrels into the reactor is performed using a suction lance and vacuum; PPE of operators consists of respiratory protection (respiratory mask with combination filter MSA, Auer 89 ABEK2), and solvent resistant protective gloves (Butoject 898).
- Use of diglyme in cryptand synthesis takes place in a closed reactor; therefore potential for exposure is only given if the different openings (manhole, bung hole, etc.) are open. The reaction product is transferred to the centrifuge in closed pipeline systems, assisted by pressurised nitrogen; solvent waste (containing diglyme) is discharged from the centrifuge into 200 L barrels which are disposed of as hazardous waste by a certified contractor. The connection and de-connection of the barrels is a manual task with exposure potential through the bung hole of the barrel.
- The barrels are disposed via the Merck internal waste management and certified contractors.

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

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

9.1. Exposure scenario 1: Use at industrial site - Solvent for Kryptofix® manufacturing

Sector of use:

SU 9, Manufacture of fine chemicals

Environment contributing scenario(s):	
Solvent for Kryptofix synthesis	ERC 4
Worker contributing scenario(s):	
Diglyme charging	PROC 8b
Addition of reaction partners	PROC 4
Transfer of diglyme from 200 l barrel to 30 l barrel	PROC 8b
[redacted] (reaction) - Addition of water/diglyme mixture	PROC 8b
Transfer of suspension to centrifuge and centrifugation	PROC 8b
Emptying of centrifuge	PROC 4
Distribution of wet crystals in the drying oven	PROC 4

9.1.1. Environmental contributing scenario 1: Solvent for Kryptofix® synthesis

9.1.1.1. Conditions of use

Amount used, frequency and duration of use (or from service life)
• Daily use at site: [redacted] tonnes/day *The maximum amount required for synthesis of Kryptofix compounds, as approved by the local authority, is [redacted] diglyme per production day. Often this amount is not exhausted for process-related reasons hence the figure of [redacted] constitutes the worst-case.*
• Annual use at a site: [redacted] tonnes/year
• Percentage of EU tonnage used at regional scale: = 100 %

Technical and organisational conditions and measures
• Exhaust air treatment: Adsorption/wet scrubber for gas removal [Effectiveness Air: 99%]
Conditions and measures related to sewage treatment plant
• On site Municipal STP: Yes [Effectiveness Water: 0.096% (based on inherent biodegradability]
• Discharge rate of STP: >= 6.9E3 m^3/d *Merck's on-site STP (Darmstadt, Germany) has a flow-rate of 0.08 m³/s, corresponding to 6912 m³/d (rounded to 6900 m³/d for the purpose of emission estimation).*
• Application of the STP sludge on agricultural soil: No
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: >= 5.7E4 m^3/d *The on-site STP discharges to a small stream named "Landgraben", with an average flow rate of 0.66 m³/s, corresponding to 57024 m³/d (rounded to 57000 m³/d for the purpose of emission estimation).*

Darmstadt (Germany) is the headquarters of Merck, the global pharmaceutical and chemical company. The Merck site encompasses 1.2 km², with approximately 9,000 employees working in research and production in the business sectors Healthcare, Life Science and Performance Materials, or in central corporate functions. The production of Kryptofix is located in a specific multi-purpose facility plant within this complex. Figure 7 shows an aerial image of the sewage treatment plant of the facility.

Figure 7: Sewage treatment plant at the Merck production facility in Darmstadt (Germany)

9.1.1.2. Releases

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

Table 10: Local releases to the environment

Release	Release factor estimation method	Explanation / Justification
Water	Release factor (Emission to wastewater, site-specific)	**Initial release factor:** 0.01% **Final release factor:** 0.01% **Local release rate:** 0.016 kg/day **Explanation / Justification:** The facility is completely separated from the wastewater stream. All solvent waste is disposed of as hazardous waste. The only release pathway to the aqueous environment is via wastewater from the scrubber used for cleaning off-gas from the LEV. Since the maximum release of diglyme due to its physico-chemical properties and type of equipment is 0.01 %, it is assumed in a worst-case approach that the entire diglyme removed from off-gas by the scrubber is directed to wastewater, i.e. the release factor to water is 0.01 %.
Air	Release factor (Emission to wastewater, site-specific, following the TGD (2003))	**Initial release factor:** 0.01% **Final release factor:** 0.01% **Local release rate:** 0.016 kg/day **Explanation / Justification:** The only emission sources are exhaust air from LEV (either process integrated, or movable capturing hoods where diglyme is transferred via small suction lances and small bung holes, 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 A 1.1: 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 (Emission to soil, site-specific)	**Final release factor:** 0% **Explanation / Justification:** All solvent waste is disposed of as hazardous waste. Release to soil does not occur.

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

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

Table 11: Exposure concentrations and risks for the environment (and man via the environment)

Protection target	Local concentration (C_{local}, PEC)	RCR
Freshwater	3.55E−04 mg/L	Not required
Marine water	3.29E−05 mg/L	Not required
Air	2.97E−07 mg/m³	Not required
Agricultural soil	1.06E−05 mg/kg dw	Not required
Man via environment – inhalation	Local PEC: 2.97E−07 mg/m³	< 0.01

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 < 0.01 (see Table 11). This risk characterisation is based on TGD defaults hence sufficiently conservative.

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. Dermal exposure is estimated using RISKOFDERM, as a Tier 2 modelling tool (reasonable worst-case). Process synthesis takes place in a closed reactor.

Inhalation exposure is estimated using ART and compared with measured data. The ART estimate and the measured data are in the same order of magnitude. The duration of the charging activity, with potential for exposure to diglyme vapours in the workplace atmosphere, is approximately 30 minutes.

For estimation of dermal exposure RISKOFDERM is used. In view of the high level of containment (closed system, with minimised possibility of surface contamination by the reaction solution) the RISKOFDERM generated dermal exposure value is a vast overestimate. For this task, no dermal exposure can be expected since the transfer hose is equipped with gas-tight connections on both the side of the reactor and of the lance placed in the bung hole of the barrel. The period of potential dermal contact is limited to removal of the suction lance from the 200 L barrel and subsequent placing in the LEV for drying. This activity takes at maximum 30 seconds. For modelling using RISKOFDERM, one minute is assumed in a worst-case approach.

9.1.2.2. Exposure and risks for workers

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

Table 12: Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	ART prediction, 90th percentile: 0.072 mg/m³ **Correction for RPE (APF 95 %): 3.6E−03 mg/m³** **Measured data:** For detailed information on measured data please see below and chapter 10.1.	RCR < 0.01
Dermal, systemic, long-term	**1.2E−02 mg/kg bw/d** (Riskofderm 2.0)	RCR = 0.05
Combined routes, systemic, long-term		RCR = 0.052

Remarks on exposure data

ART 1.5

- Inhalation, systemic, long-term:

Scenario details	
Number of activities	1
Duration (mins)	30
Total duration (mins)	480
Nonexposure period (mins)	450
Details for activity diglyme charging	
Emission sources	near field
Near-field exposure	
Operational conditions	
Substance emission potential	
Substance product type	Liquids
Process temperature	[redacted]
Vapour pressure	
Liquid mole fraction	1
Activity coefficient	1
Activity emission potential	
Activity class	Falling liquids

Situation	Transfer of liquid product with flow of 10–100 l/minute
Containment level	Handling that reduces contact between product and adjacent air
Loading type	Splash loading, where the liquid dispenser remains at the top of the reservoir and the liquid splashes.
Surface contamination	
Process fully enclosed?	No
Effective housekeeping practices in place?	Yes
Dispersion	
Work area	Indoors
Room size	300 m³
Risk Management Measures	
Localised controls:	
Primary	Low level containment (90.00 % reduction)
Secondary	No localized controls (0.00 % reduction)
Segregation	No segregation (0.00 % reduction)
Dispersion	
Ventilation rate	3 air changes per hour (ACH)

Predicted exposure is given as the 90th percentile full-shift exposure.
The ART estimate is corrected for RPE. PPE/RPE is worn during all working steps.

Measured HH (Measured exposure, diglyme charging)

- **Inhalation, systemic, long-term**

Description
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 sections 9.0.1 and 10.1.1) there were only two opportunities for air sampling.

It is also important to note that the first measurement campaign was conducted at a time when less strict RMMs were implemented: Gas-tight connections of barrels and hoses were not yet in place. This explains why some measured data are higher than the model results. The second measurement campaign was performed after new safety measures were implemented. This includes improved airtightness of fittings and tubes. Accordingly, the measured concentrations were reduced.

Results
Since the measurement periods do not exactly match the activities as described here (i.e. the WCS) and can therefore not be compared to modelling results at WCS level, all results are shown in chapter 10.1.1 in detail. The risk characterisation based on measured data is hence calculated for aggregated exposure across all activities. Due to the fact that the number of data points is insufficient for robust exposure estimation, the main risk assessment is based on modelled exposures, while the measurements are used as confirmatory data.

Riskofderm 2.0

- **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	30 L/min
Resulting exposure rate hands (90th percentile)	17 mg/min
Cumulative duration of task during a shift	1 min
Exposure loading per shift hands	16.6 mg
Use of gloves	95 % protection

Corrected exposure:	0.83 mg
Body dose (70 kg bw):	0.012 mg/kg bw/d

9.1.3. Worker contributing scenario 2: Addition of reaction partners (PROC 4)

9.1.3.1. Conditions of use

The process of adding the reaction partners, with all sub-steps including all implemented risk management measures, PPE, etc., is described in detail is section 9.0.1 above. Accordingly, the current scenario can be broken down into three sub-tasks/activities:

1. Addition of solid cryptand precursor to the reactor via the manhole (diameter = 25 cm); duration 5 minutes
2. Addition of [redacted] (Hydride Species) to the reactor via small volume orifice (diameter = 5 cm); duration 15 minutes
3. Addition of [redacted] (Boron Compound)/THF complex to the reactor (using a flexible hose and airtight connections); duration 75 minutes

The cryptand precursor is manually added in solid form to the synthesis reactor via the manhole (diameter = 25 cm). A complex of [redacted] (Boron Compound) is weighed and transferred into a barrel via a manual pump (no diglyme involved). The worker connects the barrel to the hose/pump system and initiates the dosage to the reactor by starting the dosage pump. The hose is connected to the reactor airtight, whereas the bung hole of the barrel (diameter ca. 5 cm) is covered by a cap which is not perfectly airtight but designed for restricting diffusion of vapours through this small orifice. Therefore, LEV (movable capturing hood) is placed in close proximity to the bung hole.

Addition of solid reaction partners (cryptand precursor and [redacted] (Hydride Species)) is performed manually via the different openings of the reaction chamber. There is no handling of diglyme or contact to diglyme contaminated surfaces during this process. Therefore, estimation of dermal exposure is omitted from the exposure estimation and modelling of exposure is restricted to the inhalation route. The tasks are estimated to take maximally 15 minutes. Exposure to diglyme can occur only during manual introduction of substances into the reaction chamber.

Process synthesis itself takes place in a closed reactor and is covered in WCS 4 (section 9.1.5).

In the current WCS 2, the operator does not get in contact with diglyme during the different steps. Inhalation exposure is estimated both using ART and based on measured data (the latter for confirmatory purposes only, due to low number of data points). During the activities assessed in the current contributing scenario no dermal exposure can occur, as there is no possibility of contact to diglyme. The reactants, as described above and in section 9.0.1, do not contain diglyme. Therefore, the likelihood and level of dermal exposure is negligible.

9.1.3.2. Exposure and risks for workers

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

Table 13: Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	ART prediction, 90th percentile: 0.27 mg/m³ **Correction for RPE (APF 95 %): 1.35E–02 mg/m³** **Measured data:** For detailed information on measured data please see below and chapter 10.1.	RCR = 0.008
Dermal, systemic, long-term	**No exposure – no contact to potentially contaminated surfaces**	RCR = 0
Combined routes, systemic, long-term		RCR = 0.008

Remarks on exposure data

ART 1.5

- **Inhalation, systemic, long-term:**

Scenario details	
Number of activities	1
Total duration (mins)	480
Non-exposure period (mins)	385
Details for activity diglyme charging	
Emission sources: Near field	
Duration (mins)	95
Near-field exposure	
Operational Conditions	
Substance emission potential	
Substance product type Liquids Process temperature	[redacted]
Vapour pressure	
Liquid mole fraction	1
Activity coefficient	1
Activity emission potential	
Activity class	Activities with agitated surfaces
Situation	
Open surface	< 0.1 m²
Surface contamination	
Process fully enclosed?	No
Effective housekeeping practices in place?	Yes
Dispersion	
Work area	Indoors
Room size	300 m³
Risk Management Measures	
Localised controls	
Primary	Other LEV systems (50.00 % reduction)
Secondary	No localized controls (0.00 % reduction)
Segregation	No segregation (0.00 % reduction)
Dispersion	
Ventilation rate	3 air changes per hour (ACH)

Predicted exposure is given as the 90th percentile full-shift exposure.
The ART estimate is corrected for PPE. PPE/RPE is worn during all working steps.

Measured HH (Measured exposure, addition of reaction partners)

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 sections 9.0.1 and 10.1.1) there were only two opportunities for air sampling.

It is also important to note that the first measurement campaign was conducted at a time when less strict RMMs were implemented: Gas-tight connections of barrels and hoses were not yet in place. This explains why some measured data are higher than the model results. The second measurement campaign was performed after new safety measures were implemented. This includes improved airtightness of fittings and tubes. Accordingly, the measured concentrations were reduced.

Results

Since the measurement periods do not exactly match the activities as described here (i.e. the WCS) and can therefore not be compared to modelling results at WCS level, all results are shown in chapter 10.1.1 in detail. The risk characterisation based on measured data is hence calculated for aggregated exposure across all activities. Due to the fact that the number of data points is insufficient for robust exposure

estimation, the main risk assessment is based on modelled exposures, while the measurements are used as confirmatory

9.1.4. Worker contributing scenario 3: Transfer of diglyme from 200 L barrel to 30 L barrel (PROC 8b)

9.1.4.1. Conditions of use

The process of the preparation of the [redacted] (reaction mixture), including all implemented risk management measures, PPE, etc., is described in detail is section 9.0.1 above.

Diglyme is transferred from a 200 L barrel into a 30 L barrel using a manual pump: The bung hole of the 200 L barrel is opened and a lance equipped with gas-tight connection is inserted. This step takes only a few seconds and is performed under LEV (movable capturing hood). The opposite end of the hose, still free from diglyme, is placed into the 30 L barrel via a bung hole (diameter ca. 5 cm) which is not air tight. Diglyme is transferred via a semi-automatic pump from the larger into the smaller barrel. Afterwards water is added from the internal demineralized (VE) water network. The whole process takes 2–3 minutes; a maximum of 5 minutes are assumed for exposure estimation as a worst-case.

The worker stays next to the barrels for operating the pump until all liquid is transferred. After completion of the diglyme transfer, the lance is removed from the bung hole and placed into the LEV to evaporate remaining diglyme. After drying, the diglyme-free lance is rinsed with water. During the whole activity the worker wears PPE as described above. Figure 4 shows the 200 L and 30 L drums and the manual pump which is used for diglyme transfer between barrels.

The worker stays next to the barrels until all liquid is transferred, because the pump is operated manually. Inhalation exposure is estimated using ART. For estimation of dermal exposure RISKOFDERM is used. In view of the high level of containment (closed barrels, with only very short opening times and afterwards no possibility of surface contamination by the reaction solution) both the ART and RISKOFDERM generated exposure values can be seen as a vast overestimation. In fact there is very limited potential for dermal exposure in this step The period of potential dermal contact is limited to removal of the suction lance from the 200 L barrel and subsequent placing in the LEV for drying. This activity takes at maximum 30 seconds. For modelling using RISKOFDERM, one minute is assumed in a worst-case approach.

9.1.4.2. Exposure and risks for workers

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

Table 14: Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	ART prediction, 90th percentile: 0.018 mg/m³ **Corrected for RPE (95 %): 9.0E–04 mg/m³** **Measured data:** For detailed information on measured data please see below and chapter 10.1.	RCR < 0.01
Dermal, systemic, long-term	**8.5E–03 mg/kg bw/d** (Riskofderm 2.0)	RCR = 0.035
Combined routes, systemic, long-term		RCR = 0.036

Remarks on exposure data

ART 1.5

- **Inhalation, systemic, long-term:**
  Scenario details
  Number of activities 1
  Total duration (mins) 480

Non-exposure period (mins)	475
Details for activity	
Emission sources	Far field
Duration (mins)	5
Far-field exposure	
Operational Conditions	
Substance emission potential	
Substance product type	Liquids
Process temperature	[redacted]
Vapour pressure	
Liquid mole fraction	1
Activity coefficient	1
Activity emission potential	
Activity class	Falling liquids

Situation
Transfer of liquid product with flow of 10-100 l/minute
Containment level
Handling that reduces contact between product and adjacent air.
Loading type
Splash loading, where the liquid dispenser remains on the top of the reservoir and the liquid splashes freely
Surface contamination

Process fully enclosed?	No
Effective housekeeping practices in place?	Yes

Dispersion

Work area	Outdoors
Source located close to buildings?	Yes
Worker distance	> 1 m

Risk Management Measures
Localised controls

Primary	Other LEV systems (50.00 % reduction)
Secondary	No localized controls (0.00 % reduction)
Segregation	No segregation (0.00 % reduction)
Personal enclosure	No personal enclosure

Predicted exposure is given as the 90th percentile full-shift exposure.
The ART estimate is corrected for PPE. PPE/RPE is worn during all working steps.

Measured HH (Measured exposure, diglyme charging)

- **Inhalation, systemic, long-term**

Description
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 sections 9.0.1 and 10.1.1) there were only two opportunities for air sampling.

It is also important to note that the first measurement campaign was conducted at a time when less strict RMMs were implemented: Gas-tight connections of barrels and hoses were not yet in place. This explains why some measured data are higher than the model results. The second measurement campaign was performed after new safety measures were implemented. This includes improved airtightness of fittings and tubes. Accordingly, the measured concentrations were reduced.

Results
Since the measurement periods do not exactly match the activities as described here (i.e. the WCS) and can therefore not be compared to modelling results at WCS level, all results are shown in chapter 10.1.1 in detail. The risk characterisation based on measured data is hence calculated for aggregated exposure across all activities. Due to the fact that the number of data points is insufficient for robust exposure estimation, the main risk assessment is based on modelled exposures, while the measurements are used as confirmatory data.

Riskofderm 2.0

- **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	5 L/min
Resulting exposure rate hands (90th percentile)	12 mg/min
Cumulative duration of task during a shift	1 min
Exposure loading per shift hands	11.8 mg
Correction for 100 % diglyme content in solvent waste	none
Use of gloves (95 % protection)	
Corrected exposure	0.59 mg
Body dose (70 kg bw)	0.0085 mg/kg bw/d

9.1.5. Worker contributing scenario 4: [redacted] (reaction step) – addition of water/diglyme mixture (PROC 8b)

9.1.5.1. Conditions of use

The process of the addition of water/diglyme mixture, including all implemented risk management measures, PPE, etc., is described in detail in section 9.0.1 above. A mobile LEV system is in operation during the task. Process synthesis takes place in a closed reactor.

The water/diglyme mixture (50/50, w/w), see WCS 3, is added to the reaction chamber: The worker connects the 30 L barrel to the hose/pump system that was already used for [redacted] (Boron Compound)/THF complex charging (see WCS 2) and initiates the dosage to the reactor by starting the dosage pump. The worker monitors the [redacted] (reaction) permanently and is physically present in the room for approximately 1 hour. The hose is connected to the reactor airtight, whereas the bung hole of the barrel (diameter ca. 5 cm) is covered by a cap which is not perfectly airtight but designed for restricting diffusion of vapours through this small orifice. Therefore, LEV (movable capturing hood) is placed in close proximity to the bung hole. After the reaction is complete, the tubes and lances are removed and dried by air stream in a LEV system. During these steps the worker wears the aforementioned PPE. Figure 5 illustrates the design of the connections between barrel, hose and reaction vessel.

During the semi-automatic pumping process there is no possibility of dermal exposure to diglyme because all connections are completely closed and the worker operates a semi-automatic pump from the distance of > 1 m. The only dermal exposure possibilities occur during the opening of the barrel and the insertion and removing of the lance. The steps in which the lances are removed, dripped off and placed in the suction hose are potential sources of dermal exposure. These steps are estimated to take around 5 minutes.

Inhalation exposure is estimated using ART. Dermal exposure is estimated using RISKOFDERM, as a Tier 2 modelling tool (reasonable worst-case). The diglyme exposure via inhalation was modelled over a time of approximately 60 min. Dermal exposure is only possible during the handling of the lance and the barrel and was therefore calculated only for these steps which take about 5 minutes.

9.1.5.2. Exposure and risks for workers

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

Table 15: Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	ART prediction, 90th percentile: 5.7 µg/m³ **Corrected for RPE: 2.9E–04 mg/m³** **Measured data:** For detailed information on measured data please see below and chapter 10.1.	RCR < 0.01
Dermal, systemic, long-term	**8.0E–03 mg/kg bw/d** (Riskofderm 2.0)	RCR = 0.033
Combined routes, systemic, long-term		RCR = 0.034

Remarks on exposure data

ART 1.5

- **Inhalation, systemic, long-term:**

Scenario details	
Number of activities	1
Total duration (mins)	480
Non-exposure period (mins)	420
Details for activity diglyme charging	
Emission sources	
Near field Duration (mins)	60
Near-field exposure Operational Conditions	
Substance emission potential	
Substance product type	
Liquids Process temperature	[redacted]
Vapour pressure	
Liquid mole fraction	0.5
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	Handling that reduces contact between product and adjacent air.
Loading type	Splash loading, where the liquid dispenser remains at the top of the reservoir and the liquid splashes freely
Situation	
Open surface	< 0.1 m²
Surface contamination	
Process fully enclosed?	No
Effective housekeeping practices in place?	Yes
Dispersion Work area	Indoors
Room size	300 m³
Primary	Other LEV systems (50.00 % reduction)
Secondary	No localized controls (0.00 % reduction)
Segregation	No segregation (0.00 % reduction)
Dispersion Ventilation rate	3 air changes per hour (ACH)

Predicted exposure is given as the 90th percentile full-shift exposure.
The ART estimate is corrected for PPE. PPE/RPE is worn during all working steps.

Riskofderm 2.0

- **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
Resulting exposure rate hands (90th percentile):	5 mg/min
Cumulative duration of task during a shift	5 min
Exposure loading per shift hands	23 mg
Correction for 50 % diglyme content in solvent	11.45 mg
Use of gloves (95 % protection) - Corrected exposure	0.575 mg
Body dose (70 kg bw):	8.0 µg/kg bw/d

9.1.6. Worker contributing scenario 5: Transfer of suspension to centrifuge and centrifugation (PROC 8b)

9.1.6.1. Conditions of use

The process of transferring the suspension and the centrifugation, including all implemented risk management measures, PPE, etc. is described in detail is section 9.0.1 above.

WCS 5 encompasses two steps: Transfer of the reaction suspension via permanently installed, airtight connected piping and partly via a flexible, but airtight hose and, secondly, centrifugation of the reaction mixture.

In the first step, the [redacted] and precipitated reaction mixture is transferred from the reaction chamber into the centrifuge. This process is performed using gravity, and assisted by pressurised nitrogen (0.3 bar), transferring the reaction mixture via a fixed and airtight piping from the reaction chamber to the centrifuge. There is no exposure potential for this completely closed process. The second step comprises the centrifugation of the reaction mixture. The equipment used is a link-suspended centrifuge with top discharge. This type of centrifuge is airtight during operation hence the operator does not get in direct contact with diglyme during centrifugation. The centrifuge is connected to the air exhaust system, directing the off-air to the described waste gas washing system.

However, the filtrate (diglyme/water mixture) is transferred into 200 L barrels using a pump and a filling lance connected airtight to the bung hole of the barrels. The filtrate resulting from one production batch typically corresponds to the volume of 4 barrels. Accordingly, the worker has to manually connect the hose during the changing of the barrels, taking maximally 2 minutes per barrel. The whole centrifugation task takes about 3 hours, during which the worker stays in the centrifugation room monitoring the process. After finishing the centrifugation process the centrifugation cake is washed twice, first with filtrate and afterwards with pure water, before the centrifuge is opened. Dermal exposure is very unlikely and only possible during the exchange of the barrels, as all other steps are automated.

During this step the worker wears the aforementioned PPE. LEV is an integral part of the centrifuge. Furthermore, LEV in the form of a movable capturing hood is placed in close proximity of the bung hole of the barrel.

After the centrifugation is finished and the centrifuge cleared (see next WCS), the centrifuge and the reaction chamber are automatically rinsed, without interactions of the worker, with deionised water via permanently installed tubes and the solvent is discarded. There is no inhalation or dermal exposure during this step as the system is closed airtight.

Inhalation exposure is estimated using ART. For estimation of dermal exposure RISKOFDERM is used. In view of the high level of containment (closed system, with no possibility of surface contamination by the reaction solution) the ART generated exposure value is a conservative estimation.

9.1.6.2. Exposure and risks for workers

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

Table 16: Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	ART prediction, 90th percentile: 0.14 mg/m³ **Correctedfor RPE: 7.0E–03 mg/m³** **Measured data:** For detailed information on measured data please see below and chapter 10.1.	RCR < 0.01
Dermal, systemic, long-term	**1.08E–02 mg/kg bw/d** (Riskofderm 2.0)	RCR = 0.045
Combined routes, systemic, long-term		RCR = 0.046

Remarks on exposure data

ART 1.5

- **Inhalation, systemic, long-term**

Scenario details

Number of activities	1/3
Total duration (mins)	10
Non-exposure period (mins)	300
Details for activity diglyme charging	
Emission sources	

Scenario
Transfer of suspension into centrifuge via fixed pipes
Near-field exposure
Operational Conditions
Substance emission potential

Substance product type	Liquids
Process temperature	[redacted]
Vapour pressure	
Liquid mole fraction	0.33
Activity coefficient: 1	
Activity emission potential	
Activity class	Falling liquids

Situation

Transfer of liquid product with flow of	1–10 l/minute
Surface contamination Process fully enclosed?	No
Effective housekeeping practices in place?	Yes
Dispersion Work area Indoors Room size	300 m³
Risk Management Measures Localised controls	
Primary	Medium level containment (99 %)
Secondary	No localized controls (0.00 % reduction)
Segregation	No segregation (0.00 % reduction)

Dispersion Ventilation rate 3 air changes per hour (ACH)
Predicted exposure is given as the 90th percentile full-shift exposure.
The ART estimate is corrected for PPE. PPE/RPE is worn during all working steps.

Scenario details

Number of activities	2/3
Total duration (mins)	150
Non-exposure period (mins)	300
Details for activity diglyme charging	
Emission sources	

Scenario
Centrifugation

Far-field exposure
Operational Conditions
Substance emission potential

Substance product type	Liquids
Process temperature	[redacted]
Vapour pressure	
Liquid mole fraction	0.33
Activity coefficient:	1

Activity emission potential

Activity class	Bottom loading

Situation

Transfer of liquid product with flow of	1–10 l/minute
Surface contamination Process fully enclosed?	No
Effective housekeeping practices in place?	Yes
Dispersion Work area Indoors Room size	300 m³
Risk Management Measures Localised controls	
Primary	Medium level containment (99 %)
Secondary	No localized controls (0.00 % reduction)
Segregation	No segregation (0.00 % reduction)

Dispersion Ventilation rate 3 air changes per hour (ACH)
Predicted exposure is given as the 90th percentile full-shift exposure.
The ART estimate is corrected for PPE. PPE/RPE is worn during all working steps.

Scenario details
Connection and de-connection of solvent containing barrels

Number of activities	3/3
Total duration (mins)	10
Non-exposure period (mins)	300

Activity emission potential

Activity class	Handling of contaminated objects
Situation	Activities with treated/contaminated objects (surface <0.1 m²)
Contamination level	Contamination < 10 % surface

Details for activity diglyme charging
Emission sources

Scenario Transfer of suspension into centrifuge
Far-field exposure
Operational Conditions
Substance emission potential

Substance product type	Liquids
Process temperature	[redacted]
Vapour pressure	
Liquid mole fraction	0.33

Activity coefficient: 1
Activity emission potential

Activity class	Bottom loading

Situation

Transfer of liquid product with flow of	1–10 l/minute
Surface contamination Process fully enclosed?	No
Effective housekeeping practices in place?	Yes
Dispersion Work area Indoors Room size	300 m³
Risk Management Measures Localised controls	
Primary	Other LEV system (50 % reduction)
Secondary	No localized controls (0.00 % reduction)
Segregation	No segregation (0.00 % reduction)

Dispersion Ventilation rate 3 air changes per hour (ACH)
Predicted exposure is given as the 90th percentile full-shift exposure.
The ART estimate is corrected for PPE. PPE/RPE is worn during all working steps.

Measured HH (Measured exposure, diglyme charging)

- **Inhalation, systemic, long-term**

  Description
  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 sections 9.0.1 and 10.1.1) there were only two opportunities for air sampling.

  It is also important to note that the first measurement campaign was conducted at a time when less strict RMMs were implemented: Gas-tight connections of barrels and hoses were not yet in place. This explains why some measured data are higher than the model results. The second measurement campaign was performed after new safety measures were implemented. This includes improved airtightness of fittings and tubes. Accordingly, the measured concentrations were reduced.

  Results
  Since the measurement periods do not exactly match the activities as described here (i.e. the WCS) and can therefore not be compared to modelling results at WCS level, all results are shown in chapter 10.1.1 in detail. The risk characterisation based on measured data is hence calculated for aggregated exposure across all activities. Due to the fact that the number of data points is insufficient for robust exposure estimation, the main risk assessment is based on modelled exposures, while the measurements are used as confirmatory data.

Riskofderm 2.0

- **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
Resulting exposure rate hands (90th percentile)	5 mg
Cumulative duration of task during a shift	10 min
Exposure loading per shift hands	46 mg
Correction for 33 % diglyme content in solution	15.18 mg
Use of gloves (95 % protection); corrected exposure	0.76 mg
Body dose (70 kg bw):	0.0108 mg/kg bw/d

9.1.7. Worker contributing scenario 6: Emptying of centrifuge (PROC 4)

9.1.7.1. Conditions of use

The process of the emptying of the centrifuge, including all implemented risk management measures, PPE, etc., is described in detail is section 9.0.1 above.

Solvents are removed automatically via connected tubes during the centrifugation process. After completion of the centrifugation process the centrifuge is cleared manually by a worker using a paddle, transferring the precipitated reaction product into a barrel. The step takes maximally 30 minutes and involves near-field contact of the worker to the emission source. Inhalation exposure is estimated using ART. For estimation of dermal exposure RISKOFDERM is used. The content of diglyme after centrifugation was measured to be 0.3 %.

Inhalation exposure, however, is mainly determined by the diglyme content in the liquid filtrate, instead of the diglyme residue in the solid centrifugation cake. Although the filtrate is filled into barrels for disposal (see WCS 5), the interior of the centrifuge is still moistened with filtrate. During centrifugation, duplicate rinsing with water is applied. The residual diglyme content in the resulting diglyme/water mixture is in the range of 5–10 % (“minor fraction” in ART terminology). Therefore, the ART model is configured as “activities with relatively undisturbed surfaces” (wetted inner surfaces of the centrifuge), and the surface area is assumed to be > 3 m² (highest category in ART). The worker wears full PPE (chemical protective suit, protective gloves, RPE). It is noteworthy that the filter of the full face mask is attached dorsally, in order to maximise the distance between the emission source and

the breathing zone. This safety measure is, however, difficult to implement in the ART model, which is therefore configured under the assumption of near-field exposure in a worst-case approach.

9.1.7.2. Exposure and risks for workers

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

Table 17: Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	ART prediction, 90th percentile: 54 mg/m³ **Corrected for RPE (95 %): 2.7E–02 mg/m³** **Measured data:** For detailed information on measured data please see below and chapter 10.1.	RCR = 0.016
Dermal, systemic, long-term	**3.0E–04 mg/kg bw/d** (Riskofderm 2.0)	RCR 0.01
Combined routes, systemic, long-term		RCR < 0.01

Remarks on exposure data

ART 1.5

- *Inhalation, systemic, long-term*

Scenario details Number of activities	1
Total duration (mins)	480
Non-exposure period (mins)	450
Details for activity	Emptying of centrifuge
Emission sources	
Near field Duration (mins)	30
Near-field exposure Operational Conditions	
Substance emission potential	
Substance product type	Liquids
Process temperature	[redacted]
Vapour pressure	
Liquid mole fraction	Minor (5–10 %)
Activity coefficient	1
Activity emission potential	
Activity class	Activities with relatively undisturbed surfaces (no aerosol formation)
Situation	Open surface > 3.0 m²
Surface contamination	
Process fully enclosed?	No
Effective housekeeping practices in place?	Yes
Dispersion Work area	Indoors
Room size	300 m³
Risk Management Measures	
Localised controls Primary	No localized controls (0.00 % reduction)
Secondary	No localized controls (0.00 % reduction)
Dispersion	
Ventilation rate	3 air changes per hour (ACH)

Predicted exposure is given as the 90th percentile full-shift exposure.
The ART estimate is corrected for PPE. PPE/RPE is worn during all working steps.

Measured HH (Measured exposure, diglyme charging)

- **Inhalation, systemic, long-term**

Description
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 sections 9.0.1 and 10.1.1) there were only two opportunities for air sampling.

It is also important to note that the first measurement campaign was conducted at a time when less strict RMMs were implemented: Gas-tight connections of barrels and hoses were not yet in place. This explains why some measured data are higher than the model results. The second measurement campaign was performed after new safety measures were implemented. This includes improved airtightness of fittings and tubes. Accordingly, the measured concentrations were reduced.

Results
Since the measurement periods do not exactly match the activities as described here (i.e. the WCS) and can therefore not be compared to modelling results at WCS level, all results are shown in chapter 10.1.1 in detail. The risk characterisation based on measured data is hence calculated for aggregated exposure across all activities. Due to the fact that the number of data points is insufficient for robust exposure estimation, the main risk assessment is based on modelled exposures, while the measurements are used as confirmatory data.

Riskofderm 2.0

- **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
Resulting exposure rate hands (90th percentile)	5 mg/min
Cumulative duration of task during a shift	30 min
Exposure loading per shift hands	137 mg
Correction for 0.31 % diglyme content in solvent waste	0.427 mg
Use of gloves (95 % protection); corrected exposure	0.02 mg
Use of chemical protective suit	Tychem® F Standard
Body dose (70 kg bw)	0.3 µg/kg bw/d

9.1.8. Worker contributing scenario 7: Distribution of wet crystals in the drying oven (PROC 4)

9.1.8.1. Conditions of use

The process of the distribution of the crystals in the drying oven, including all implemented risk management measures, PPE, etc., is described in detail is section 9.0.1 above.

The final step includes the transfer and spreading of the precipitated reaction product, containing approximately 0.3 % diglyme, to the oven where remaining solvent is evaporated [redacted]. Inhalation exposure is estimated using ART. For estimation of dermal exposure RISKOFDERM is used.

9.1.8.2. Exposure and risks for workers

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

Table 18: Exposure concentrations and risks for workers

Route of exposure and type of effects	Exposure concentration	Risk characterisation
Inhalation, systemic, long-term	ART prediction, 90th percentile: 0.022 mg/m³ **Correctedfor RPE (APF 95 %): 1.1E−03 mg/m³** **Measured data:** For detailed information on measured data please see below and chapter 10.1.	RCR < 0.01
Dermal, systemic, long-term	**2.9E−03 mg/kg bw/d** (Riskofderm 2.0)	RCR = 0.012
Combined routes, systemic, long-term		RCR = 0.013

Remarks on exposure data

ART 1.0

- **Inhalation, systemic, long-term:**

Scenario details	
Number of activities	1
Total duration (mins)	480
Non-exposure period (mins)	450
Details for activity	Distribution of wet crystals in the drying oven
Emission sources	
Near field Duration (mins)	30
Near-field exposure	
Operational Conditions	
Substance emission potential	
Substance product type	Liquids
Process temperature	[redacted]
Vapour pressure	
Liquid mole fraction	0.0031
Activity coefficient	1
Activity emission potential	
Activity class	Handling of contaminated objects
Situation	Activities with treated/contaminated objects (surface > 3 m²)
Surface contamination	Contamination > 90 % of surface
Process fully enclosed?	No
Effective housekeeping practices in place?	Yes
Dispersion	
Work area	Indoors
Room size	300 m³
Risk Management Measures	
Localised controls	
Primary	No localized controls (0.00 % reduction)
Secondary	No localized controls (0.00 % reduction)
Dispersion Ventilation rate	3 air changes per hour (ACH)

Predicted exposure is given as the 90th percentile full-shift exposure.
The ART estimate is corrected for PPE. PPE/RPE is worn during all working steps.

Riskofderm 2.0

- **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	More than rare contact
Kind of skin contact with the contaminant	More than 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
Resulting exposure rate hands (90th percentile)	44 mg/min
Cumulative duration of task during a shift	30 min
Exposure loading per shift hands:	1313 mg
Correction for 0.31 % diglyme content in solvent waste:	4.07 mg
Use of gloves (95 % protection); corrected exposure:	0.204mg
Use of chemical protective suit	Tychem® F Standard
Body dose (70 kg bw):	2.9 µg/kg bw/d

10. RISK CHARACTERISATION RELATED TO COMBINED EXPOSURE

10.1. Human health

10.1.1. Workers

10.1.1.1. Modelled exposure

The use that is applied for, diglyme used as solvent in manufacturing of cryptand intermediates, has been divided into 7 WCSs. Activities described in WCS 1–7 are performed by the same workers in the course of a regular shift. However, the process runs over two consecutive days. Activities described in WCS 1–3 are performed on day 1, the remainder (WCS 4–7) on day 2. Accordingly, all the WCS described in this CSR are expected to contribute to combined exposure, however activities need to be considered on day 1 and 2 separately. Combined exposure is estimated by simple adding up of all WCS-specific exposure estimates for both the inhalation and the dermal route on day 1 and 2, respectively. Combined exposures including risk characterisation are presented in Table 19 and Table 20.

Table 19: Overview of combined and independent worker inhalation exposure to diglyme

Scenario		Day	Exposure estimate (ART 1.5, corrected for RPE)	Risk characterisation (inhalation)
WCS 1	Diglyme charging, PROC 8b	1	3.6E−03 mg/m³	RCR < 0.01
WCS 2	Addition of reaction partners, PROC 4	1	1.35E−02 mg/m³	RCR = 0.008
WCS 3	Transfer of diglyme from 200 L barrel to 30 L barrel, PROC 8b	1	9.0E−04 mg/m³	RCR < 0.01
Sum day 1 (WCSs 1–3)			**1.80E−02 mg/m³**	**RCR = 0.011**
WCS 4	[redacted] (reaction step) – addition of water/diglyme mixture, PROC 8b	2	2.9E−04 mg/m³	RCR < 0.01
WCS 5	Transfer of suspension to centrifuge and centrifugation, PROC 8b	2	7.0E−03 mg/m³	RCR < 0.01
WCS 6	Emptying of centrifuge, PROC 4	2	2.7E−02 mg/m³	RCR = 0.016
WCS 7	Distribution of wet crystals in the drying oven, PROC 4	2	1.1E−03 mg/m³	RCR < 0.01
Sum day 2 (WCSs 4–7)			**3.54E−02 mg/m³**	**RCR = 0.02**

Table 20: Overview of combined and independent worker dermal exposure to diglyme

Scenario		Day	Exposure estimate (Riskofderm 2.0)	Risk characterisation (dermal)
WCS 1	Diglyme charging, PROC 8b	1	1.2E−02 mg/kg bw/d	RCR = 0.052
WCS 2	Addition of reaction partners, PROC 4	1	No exposure – no contact to potentially contaminated surfaces	RCR = 0.0
WCS 3	Transfer of diglyme from 200 L barrel to 30 L barrel, PROC 8b	1	8.5E−03 mg/kg bw/d	RCR = 0.035
Sum day 1 (WCSs 1–3)			**2.05E−02**	**RCR = 0.085**
WCS 4	[redacted] (reaction step) – addition of water/diglyme mixture, PROC 8b	2	8.0E−03 mg/kg bw/d	RCR = 0.033
WCS 5	Transfer of suspension to centrifuge and centrifugation, PROC 8b	2	1.08E−02 mg/kg bw/d	RCR = 0.045
WCS 6	Emptying of centrifuge, PROC 4	2	3.0E−04 mg/kg bw/d	RCR < 0.01
WCS 7	Distribution of wet crystals in the drying oven, PROC 4	2	2.9E−03 mg/kg bw/d	RCR = 0.012
Sum day 2 (WCS 4-7)			**2.2E−02 mg/kg bw/day**	**RCR = 0.09**

The relevant combined risk characterisations (aggregated over discrete WCS on day 1 and 2, respectively) for combined routes (inhalation and dermal) are calculated as follows, based on the overview given in Table 19 and Table 20:

Day 1 (inhalation + dermal): RCR = 0.096

Day 2 (inhalation + dermal): RCR = 0.11

Combined exposure estimates and risk characterisations are almost equivalent for days 1 and 2. The average daily risk characterisation can thus be given as:

RCR = 0.103

10.1.1.2. Measured exposure data

Merck performed efforts during the last months to accompany synthesis campaigns by exposure measurements for the purpose of this AfA. Measurements of airborne residues during diglyme charging were specifically conducted with the aim of supporting this application for authorisation. This includes fixed sampling positions within the room and mobile (personal) sampling points attached to the workers and collecting air from the workers' breathing zone. Two operators were fitted with active samplers and two stationary measurements were performed in parallel. The values presented in the following represent the time-weighted average full-shift exposure concentrations, for both the stationary and the personal measurements, i.e. they were corrected for the duration of the sampling period. The measured values do not consider RPE which is, however, always worn when performing activities that could lead to potential diglyme exposure. Correction for RPE is additionally presented in the tables below, where appropriate.

As already briefly explained in CSR chapter 9, measured data are presented at this point (chapter 10.1) since not all measurement periods coincide with the WCSs. For example, the activities "transfer of suspension to centrifuge and centrifugation" (WCS 5) and "emptying of centrifuge" (WCS 6) were covered by one continuous air sampling period. Therefore, the corresponding measurement values are not directly comparable with WCS-based modelled exposure estimates.

Furthermore, only a limited number of measured values are available, not fulfilling the requirements for the sample size necessary to serve as basis for exposure estimation ($n \geq 6$ measurements per activity). Therefore, measured data are presented as supportive data, aimed at confirming the modelling results. The risk characterisation hence is based on modelled exposures.

10.1.1.2.1 First measurement during synthesis campaign in April 2015

During the synthesis campaign on 16./20./21. April 2015 measurement with stationary and mobile (personal) sampling points were performed. The results are shown in Table 21 and Table 22. .

It is also important to note that the first measurements in April 2015 were conducted at a time when less strict RMMs were implemented: Gas-tight connections of barrels and hoses were not in place on all containers. This explains why measured data in this first measurement campaign are approximately a factor 5 higher than the modelled results.

As only a few production campaigns are performed during the year and due to the fact that the different steps were not entirely identical with the WCS in this document, these measurements were seen as supportive information for this AfA and the data from the first measurement campaign are not processed further: No aggregated exposures and no RCRs are calculated – the comparison with modelled exposures is restricted to data from the second measurement campaign, see below.

Table 21: Stationary measuring values from the first measurement campaign

Activity No.	Sampling duration [min]	Sampling volume [m³]	Time weighted average full-shift exposure [mg/m³]
2	30	0.024	0.009
2	30	0.024	0.025
5, 6	60	0.048	0.05
5, 6	60	0.048	0.029
7, 8	160	0.128	0.025
7, 8	160	0.128	0.031

Table 22: Personal measuring values from the first measurement campaign

Activity No.	Sampling duration [min]	Sampling volume [m³]	Time weighted average full-shift exposure [mg/m³]
2	30	0.024	0.012
2	30	0.024	0.013
5,6	60	0.048	0.084
5,6	60	0.048	0.125
8	15	0.012	0.06
8	15	0.012	0.063

Activities:
(1) Weighing of [redacted] (Boron compound) (no exposure to diglyme)
(2) Charging of diglyme
(3) Addition of Kryptofix/NaI-complex
(4) Addition of [redacted] (Hydride Species)
(5) Addition of [redacted] (Boron compound) (no exposure to diglyme)
(6) Rinsing of dosing device with THF (no exposure to diglyme)
(7) Transfer of suspension to centrifuge, separation of centrifugation cake etc.
(8) Clearance of centrifuge

Sampling conditions

Stationary air sampling was conducted at a height of approx. 1.6 m and in direct proximity to the employees, and personal measurements ensured sampling of air in the breathing zone.

The sampling was carried out in accordance with the German "BIA - Arbeitsmappe 'Messung von Gefahrstoffen'", the general basic principles for the measurement of hazardous substances in the air at the workplace, reference number 0210, the general specifications for the measuring method, reference number 0250, and the specifications for sampling pumps, reference number 0260.

10.1.1.2.2 Second measurements during the production campaigns in February 2016

In February 2016 a Kryptofix® production campaign was performed and personal and stationary measurements were performed again. As described above, the activity numbers of the measurements performed do not completely match with the WCS defined in this AfA. This is due to technical limitations and the fact that the WCS have been slightly adapted during the preparation of the AfA. However, the measurements cover all processes of diglyme handling by the worker and potential exposure and the summarized exposure levels represent the realistic conditions of the use of diglyme at Merck.

Air sampling for the workplace measurement of diglyme was conducted in dependence on method MDHS 50, HSE (1985) (adsorption to Tenax; thermal desorption; GC-MSD).

Table 23: Measurements from 11. + 12. February 2016 (second measurement campaign); limit of detection (LOD): 0.0001–0.002 mg/m³, depending on sampled air volume

Activity	Location	Day	Time weighted average full-shift exposure [mg/m³] (n = 2)	Corrected for RPE (95 % reduction) [mg/m³]	RCR	Duration of exposure [h]
2,3,8	Stationary	1	0.015	0.00075		0.3
4		1	0.002	0.0001		0.2
Sum day 1			**0.017**	**0.00085**	**0.0035**	**0.5**
9		2	0.002	0.0001		1
7		2	0.135	0.00675		3
10		2	0.029	0.00145		0.5
11		2	0.0004	0.00002		0.5
Sum day 2			**0.166**	**0.0083**	**0.035**	**4.0**
2,3,8	Personal	1	0.042	0.0021		0.3
Sum day 1			**0.042**	**0.0021**	**0.0088**	**0.3**
9		2	0.008	0.0004		1
10		2	0.088	0.0044		0.5
11		2	0.003	0.00015		0.5
Sum day 2			**0.126**	**0.0063**	**0.0026**	**2.0**

Remark:

Activities (4) and (7) were measured stationary only.

Table 24: Measurement from 16. + 17. February 2016 (second measurement campaign) ; limit of detection (LOD): 0.0001–0.002 mg/m³, depending on sampled air volume

Activity	Location	Time weighted average full-shift exposure [mg/m³] (n = 2)	Corrected for RPE (95 % reduction) [mg/m³]	RCR	Duration of exposure [h]
2, 3, 8	Stationary	0.031	0.00155		0.3
5		0.025	0.00125		1.0 **
Sum day 1		**0.056**	**0.0028**	**0.017**	**1.3**
9		0.003	0.00015		1
7		0.056	0.0028		3
10		0.005	0.00025		0.5
Sum day 2		**0.064**	**0.0032**	**0.0019**	**4.5**
2,3,8	Personal	0.03	0.0015		0.3
5		0.031	0.00155		1.0 **
Sum day 1		**0.061**	**0.0031**	**0.0018**	**1.3**
9		0.001	0.00005		1
7		0.049	0.00245		3
10		0.09	0.0045		0.5
11		0.001	0.00005		0.5
Sum day 2		**0.141**	**0.0071**	**0.0042**	**5.0**

Remarks:

**) For activity (5) adding of the [redacted] (Boron compound) (no exposure to diglyme) a maximum shift mean value at a duration of the activity of 1.0 h was calculated.

Activity (11) was measured personal only.

Activities:

(1) Weighing of [redacted] (Boron compound) (no exposure to diglyme)
(2) Charging of diglyme
(3) Addition of Kryptofix/NaI-complex
(4) Addition of [redacted] (Hydride Species)
(5) Addition of [redacted] (Boron compound) (no exposure to diglyme)
(6) Rinsing of dosing device with THF (no exposure to diglyme)
(7) Transfer of suspension to centrifuge, separation of centrifugation cake etc.
(8) Transfer of diglyme to 30 l barrel
(9) Dosing of diglyme/water-mixture
(10) Clearance of centrifuge
(11) Distribution of wet crystals in the drying oven

History of workplace measurements:

The production of Kryptofix 221/222 was launched at the site in 2013 (permission according to the German federal emissions ordinance (BImschV) as of September 2012). In the course of the production launch a risk assessment was carried out. The assessment, the efficacy check of protective measures respectively, did not lead to the necessity for a measuring proof regarding the compliance with the threshold e.g. through work place measurements according to TRGS 402. Recently conducted measurements confirm this former assessment. The work place threshold of the TRGS 900 of 28 mg/m³ is clearly undershot. As no substantial changes of the relevant boundary conditions according to TRGS 402 occurred since the launch of production, no update of the risk assessment or adaptation of protective measures was necessary yet.

10.1.1.2.3 Comparison of combined modelled and measured exposures

For the purpose of assessing the adequacy of exposure modelling, measured and modelled exposures are compared in Table 25. As explained above, this comparison is only feasible for combined inhalation exposures across all WCSs. Measured dermal exposures are not available.

Table 25: Comparison of combined modelled inhalation exposures with measured airborne values from the second measurement campaign

Scenario	Modelled exposure [mg/m³] *	Exposure based on personal measurements [mg/m³] *	
		11th/12th Feb 2016	16th/17th Feb 2016
Combined WCS 1–3 (day 1)	0.0180	0.0021	0.0031
Combined WCS 4–7 (day 2)	0.0354	0.0063	0.0071

*) corrected for RPE

Conclusion: Modelled and measured exposures are in the same order of magnitude. Moreover, the modelled exposures are more conservative than the corresponding time-averaged full shift measured exposure values. Therefore, in view of the conservative nature of the modelling results as confirmed by the measured values, the risk characterisation can be considered to be sufficiently robust for demonstrating that the risks arising from the use of diglyme in the synthesis of cryptand intermediates are adequately controlled.

10.1.2. Consumer

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 environments from all exposure scenarios addressed.

Table 26: 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	0.39 kg/year
Air	0.39 kg/year
Soil	0 kg/year

10.2.1.2. Regional exposure

Remarks:

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

10.2.2. Local exposure due to all wide dispersive uses

The current application for authorisation deals with one particular use only. The assessed use is industrial use as solvent in the manufacture of cryptands 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 cryptands only.