# CHEMICAL SAFETY REPORT

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|---|---|
| **Substance Name:** | 1,2-dichloroethane (Ethylene Dichloride, EDC) |
| **EC Number:** | 203-458-1 |
| **CAS Number:** | 107-06-2 |
| **Applicant:** | Eli Lilly S.A. Irish Branch |
| **Use applied for:** | Industrial use as a reaction medium and a solvating agent in mediating subsequent chemical transformation reactions leading to the manufacture of an Active Pharmaceutical Ingredient, Raloxifene Hydrochloride |

# 9. EXPOSURE ASSESSMENT

## 9.0. Introduction

### 9.0.1 Process description.

The applicant's use of EDC is restricted to one site at Kinsale, Ireland (address: Dunderrow, Kinsale, Co. Cork, Ireland). EDC is used as a reaction medium and solvating agent in the chemical synthesis of the final intermediate in the reaction sequence used to manufacture 6-hydroxy-2-(4-hydroxyphenyl)-benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone (Raloxifene Hydrochloride). Raloxifene Hydrochloride is the Active Pharmaceutical Ingredient (API) of the Selective Estrogen Receptor Modulator (SERM) marketed by Eli Lilly under the trade name Evista®. Whilst EDC is used in the manufacturing process, it is removed from the API prior to formulation so that patient safety requirements are met. Since the residual amount of EDC in the API is safety-limited by the EMA (Euroepan Medicines Agency) (Guideline for Residual Solvents), in practice virtually all the EDC used during manufacture would be present in the production waste streams that are then disposed of in accordance with local environmental regulations. Manufacturing is on a campaign basis. There is a single campaign per year typically lasting 3 months. A schematic overview of EDC handling operations is presented in Figure 1 with a full process description, including identification of stages with and without exposure of workers, also presented. More detailed information on equipment trains and associated processes can be found in local site documentation such as P&IDs (piping & instrumentation diagrams), PFDs (process flow diagrams) and procedures.

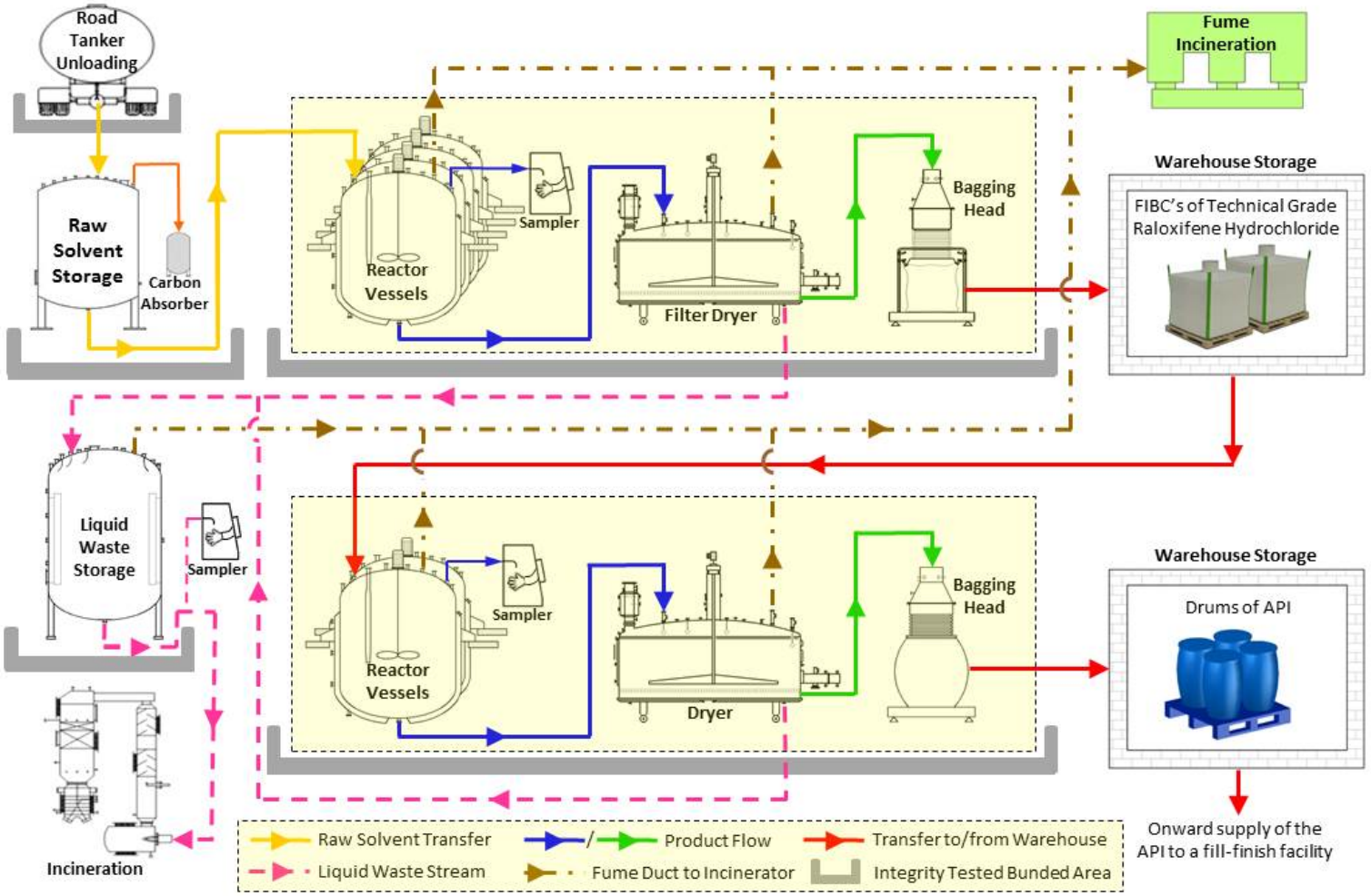
#### *Delivery – Unloading & Sampling of Road Tankers*

EDC (liquid) is supplied by road tanker, each delivery contains approximately 27,000 litres of solvent. The connection of a pressurised supply of nitrogen to the road tanker during the unloading process, use of flexible hoses with dry lock couplings and a pumped transfer ensures that this operation occurs within a closed system (see Figure 1, Appendix 6). Collection of a goods receipt sample, which is via a contained sampling device attachment, occurs shortly after arrival of the road tanker on site. Post confirmation of sample approval from the QC laboratory, the transfer of the contents of the road tanker into the raw solvent storage tank begins; it will take approximately 90 minutes to complete this operation. Also during the unloading process the displacement volume of the EDC storage tank is routed to a carbon absorber which is dedicated to the collection of gaseous discharges from this tank. When the road tanker is empty, the system is flushed with nitrogen before the hoses are disconnected.

#### *Storage of Raw Solvent*

Storage of raw solvent takes place within a closed system. The EDC storage tank (see Figure 2, Appendix 6) is located in the site bulk storage bunded area. Twice per day the operative will walk through the bunded area to conduct visual inspections of plant and equipment to ensure that these are operational and that containment measures are being maintained. Since bulk solvent is pumped from storage tank to the point of use in the manufacturing building via automated transfers, with the exception of maintenance activities, filter changes and tank sampling, exposure to workers is minimal. As per site QC requirements each tank is sampled once per quarter. All tanks have a screwed bottle type in-line sampling device and solvent filter (see Figure 3, Appendix 6). Filters are used on the sample lines of storage tanks to aid in getting a representative sample. As per site QC requirements, the filter on the sample line of each tank is changed every 12 months.

*Figure 1 – Schematic Overview* of EDC Handling Operations from Receipt of Raw Solvent to Destruction of Waste Streams by On-Site Incineration*




* This diagram, which is intended to be an illustration of the main input and outputs of the EDC handling process should be read in conjunction with the accompanying process description in Section 9.0.1

### *Chemical Synthesis of Active Pharmaceutical Ingredient*

EDC is used in the manufacture of the final intermediate referred to as technical grade Raloxifene Hydrochloride (Raloxifene Hydrochloride Technical), which is isolated in the solid form as a crystalline solvate and packaged into flexible intermediate bulk containers (FIBCs) (see Figure 4, Appendix 6). After storage in the site warehouse the technical grade Raloxifene Hydrochloride is used in the final processing step which results in the conversion to the desired non-solvated crystal form of the API.

EDC is used as a solvent to mediate three chemical reaction transformation steps: a chlorination reaction (temperature range A °C); an acylation reaction (temperature range A °C) and a de-alkylation reaction (temperature range A °C). The resulting reaction mixture is then quenched (temperature range A °C) with a heated mixture of alcohol solvents (A ). When quenching is performed in this manner, Raloxifene Hydrochloride crystallises from the resulting mixture, as a hemi solvate of EDC. The crystallisation slurry is cooled and then filtered on a Filter Dryer. The product is washed with alcohol to displace any mother liquor before it is dried and isolated. The majority of the EDC remains in the mother liquor. Collection and treatment of the filtrate/mother liquor from the process is an automated process. Mother liquors are highly acidic and must be treated with a base to pH of 5-7 before pumped transfer into the contained liquid waste system. Solid material obtained from this filtration process is referred to as technical grade Raloxifene Hydrochloride, which is packaged via a contained discharge method into FIBCs. The EDC composition of the Raloxifene Hydrochloride Technical is approximately A w/w. In this crystalline solid state Raloxifene Hydrochloride and EDC are intimately bound together. The EDC present in the technical grade Raloxifene Hydrochloride is essential to the maintenance of the crystal structure and is in a non-volatile state during storage.

In the final processing step, the technical grade Raloxifene Hydrochloride (EDC solvate) is dissolved in an A . A distillation step (temperature range A °C) is then performed which removes EDC. The distillate containing EDC is pumped into the site liquid waste storage tanks pending incineration, whilst the Raloxifene Hydrochloride product slurry remains in the distillation vessel for further processing. Final product analysis of the API Raloxifene Hydrochloride includes testing for residual EDC which must be removed to below a regulatory specification[5] of <5ppm. The API is stored in drums in the warehouse prior to shipment (see Figure 5, Appendix 6).

Addition of all raw materials including EDC to the reaction vessels is via contained transfer systems. The chemical transformation reactions involving the use of EDC leading to the formation of the technical grade Raloxifene Hydrochloride, take place in A Gallon (see Figure 6, Appendix 6) glass lined reactors, which are connected via closed distribution lines. Exhaust gases from reaction vessels are routed to primary abatement systems such as condensers and scrubbers before final treatment in the onsite fume incinerator. The monitoring of critical operational controls such as temperature, pressure and tank levels is carried out by the Distributed Control System (DCS). Hardwired or software interlocks can be used to control unit operations ensuring that pre-programmed parameters are monitored remotely from computerised panels in a control room (see Figure 7, Appendix 6). Operator exposure to EDC during routine manufacturing operations is minimal. The only task involving EDC handling is the collection of QC samples (approx. once per day) from the reaction vessels. The design of the sampler and the installation of an isolator ensures that a closed system is maintained for this task (see Figure 8, Appendix 6)).

[5] Guideline of the International Conference of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): ICH Guideline Q3C (R5) (2011): “Impurities: Guideline for Residual Solvents” gives a limit value of <5ppm for EDC.

### *Maintenance and Cleaning*

Routine maintenance tasks on manufacturing equipment are not scheduled during the production campaign for safety and productivity reasons. Therefore, the frequency of these activities is once per year.

Before a manufacturing campaign can commence essential equipment checks e.g. pressure testing, solvent flushing, filter changes etc. must take place. This process, which is referred to as the 'Rig Prep' is divided into two steps, equipment checks and flushing followed by a solvent run. The specific sequence of operations, safety instructions including PPE (Personal Protective Equipment) requirements are documented in the 'Rig-Prep' ticket. Initial flushing of equipment with EDC involves multiple short duration tasks: connection/disconnection of flexible hoses; collection of solvent samples from reaction vessels; draining the small sections of piping which cannot be blown dry with nitrogen into portable containers. It is then necessary to test the batch receipe on the Distributed Control System. This essentially is a 'dummy run' of the production process using only the raw solvents. A solvent run involves multiple short duration tasks: collection of solvent samples from reaction vessels and filter changes.

Manufacturing equipment cleaning takes place at the end of each campaign. Therefore, the frequency of these activities is once per year. Special instruction for the end of campaign cleanup including flushing instructions and PPE requirements are documented in the 'turnaround' ticket. Tanks and pipework including valves are flushed with A solution and water then blown dry with nitrogen before opening under a line-break permit. Whilst the clean-in-place system is very effective at cleaning the internal surfaces of the reaction vessels, valves must be taken apart so that component parts can be manually cleaned of any solids residue. Absorbant matting is used to contain the small amount of residual cleaning solution likely to be present.

### *Laboratory Analysis of Sample Material*

The 'in-process' laboratory analyst is responsible for the analysis of raw solvent and reaction completeness samples which takes place in designated fumehoods within the laboratory (see Figure 9, Appendix 6). Transfer of material from the sample bottle into smaller vials for analysis is conducted within the fumehood. Open handling of chemicals on lab benches is not permitted. When all tests are complete, surplus sample material is disposed of in the sample sink, which is located within a laboratory fumehood and piped into the liquid waste system. The empty sample bottle and cap is placed in a waste drum for incineration. The HVAC system serving the laboratory has a dedicated air handling unit so that there is 100% fresh air supply with 20 to 30 air exchanges per hour. Exhaust air from the fumehoods is not re-circulated. Discharge from fumehood exhaust stacks are considered minor emission points and don't require abatement, since quantities handled are so small.

### *Waste Storage and Treatment*

The liquid waste stream containing EDC is generated from mother liquors and equipment washes during the preparation of the crystalline solvate molecule. The distillate from the subsequent recrystallation step contains a small amount of EDC from the technical grade Raloxifene Hydrochloride material (approximately A kg per batch). Liquid waste streams are pumped to storage tanks via fixed piping and destroyed by an on-site incinerator. Gaseous emissions from manufacturing equipment (tanks, dryers, vacuum pumps, and scrubbers) are ultimately collected via a fume duct for on-site destruction in a fume incinerator. Both incineration facilities operate under Environmental Protection Agency (Ireland) license Number P0009-03. This requires the liquid waste incineration unit to be operated under the conditions of the Waste Incineration Directive (2000/76/EC) as amended by Directive 2010/75/EU thus meeting all associated air and water emission limit values. Fume incinerator emissions meet emission limit values for installations and activities using organic

solvents as per Annex 7 of the Industrial Emissions Directive 2010/75/EU. For more information on the design features of these incineration units see Section 9.0.4.3 ("Exposure of Humans via the Environment").

Since EDC containing waste is pumped from the manufacturing building to the liquid waste storage tanks and onwards to the incineration unit via automated transfers, with the exception of maintenance activities, filter changes and tank sampling (as described in the respective contributing scenarios), exposure to workers is minimal.

Due to site production schedule demands there is daily variation in the solvent composition of the liquid waste stream feeding the incineration unit. One of the daily routine tasks undertaken by EC&U (Environmental Control and Utilities) operative supporting the waste incineration facility, is the collection of a sample from the incineration feed tanks. There are two incineration feed tanks, one for high calorific value waste (primary waste) and one for low calorific value waste (secondary waste). Secondary waste is mostly water based (water composition 80-95%) with a typical EDC composition of <1%. Peak EDC loading of the primary waste system occurs during the Raloxifene Hydrochloride Technical manufacturing campaign with typical EDC composition in the range 5-15%. In the remaining 6-9 months of the year when Raloxifene Hydrochloride Technical liquid waste stream has cleared the storage system typical EDC composition is <1%. Samples are collected in septum top glass bottles from an in-line needle type sampler, which is located within a glovebox (see Figure 10, Appendix 6). Analysis of the sample takes place in the environmental control laboratory. Installed on the incinerator feed line is a pre-filtration unit to break up any solids and a nylon by-pass filter in sequence to prevent the incinerator guns from blocking. EC&U operative is also responsible for the cleaning and operation of this unit. Cleaning of the pre-filtration unit and the filter change out take place within a glovebag (see Figure 11, Appendix 6).

EDC contaminated solid waste generated during the use of this solvent is confined to used empty sample jars, discarded filters, soiled PPE and cleaning materials. This waste is shipped offsite as hazardous waste for incineration. The waste is classified for transport, segregated, packaged, sealed, labeled and stored on site in appropriate storage facilities pending its shipment by an approved waste contractor to an approved incineration facility. The incineration facility used must be permitted for the disposal of the particular waste streams as identified by the European Waste Catalogue (EWC ) code. The main EWC codes used for this type of waste are 07 05 13* (solid wastes from manufacture of pharmaceuticals containing dangerous substances) and 15 01 10* (waste packaging; absorbents, wiping cloths, filter materials and protective clothing contaminated by dangerous substances).

## 9.0.2 Workers involved in use of EDC

**Organisational Measures – PPE (Personal Protective Equipment)**

Workplace risk assessments are conducted on all operations to identify the existence of potential hazards. PPE is only intended to provide a minimum level of protection to workers when existing engineering and administrative controls do not suffice, or their use is not feasible.

Methods used to communicate essential chemical hazard information and associated PPE requirements to employees include production tickets, standard operating procedures, work instructions, signs and information posters. A combination of computer based and practical hands-on training is provided to all new or re-assigned employees prior to using PPE (including gloves). Employees required to wear negative pressure respirators are medically approved and face fit tested. Quantitative face fit testing is provided to employees prior to using full face cartridge respirators. With the exception of the full face cartridge respirator, disposable RPE (Respiratory Protective Equipment) is used to minimise functionality checks and the potential for inadvertent contamination if the equipment is not decontaminated correctly after use.

Proper PPE use, storage and availability are periodically evaluated during local area, activity and permit auditing processes. In addition to these well-established auditing processes, a behavioural safety programme proactively encourages workers to address deficiencies in or non-adherence to PPE requirements using an electronic reporting tool.

**Organisational Measures - Training**

Critical to ensuring that EDC is handled only by fully trained personnel is the implementation of the site training system. Training requirements are assigned to individuals via curricula containing logical groupings of courses based on job description. The curricula is assigned to individuals from their Individual training plan (ITP). Line managers are responsible for ensuring that all personnel who work within their area of responsibility are assigned an appropriate ITP that corresponds with their assigned duties and defines the training required to independently perform job duties.

Environmental, Health & Safety (EHS) training requirements covering the applicable hazards, processes or operations are summarized in the EHS training matrix, which covers all personnel handling the substance including personnel involved in cleaning and maintenance activities. As per the current EHS matrix, general chemical hazard awareness training covering potential health effects including carcinogens is provided to employees. Also, instructions on handling dangerous chemicals are also covered in major accident or process safety awareness training, as the facility is a top tier Seveso site. Both of these foundation type courses are provided to all employees on a three year frequency. Specific courses covering all chemical agents handled in an area are also provided. Task specific on-the-job training is provided for department procedures, skills, processes, equipment, instruments, or systems associated with an individual's assigned job duties via area/process specific curricula.

**Shift Pattern**

Manufacturing of Raloxifene Hydrochloride Technical and use of EDC is not carried out continuously at the plant. The manufacturing facility is only partly utilised for the production of the technical API. Raloxifene Hydrochloride Technical is manufactured in a A production campaign, which takes approximately 3 months to complete. The production plant and associated support areas run on a two 12-hour shift pattern (day shift and night shift). Employees work four 12-hour shifts and are then given 4 days off. Shift rotation is followed, so no employee works only days or only nights. The total number of 12-hour shifts for an employee at the Kinsale plant is 183 per year, which, taking holidays into account, translates to ca. 38.2 hours of work per week or 166 shifts per year. With the exception of the contract maintenance fitters, all employees work this two-shift pattern. Generally, rest break entitlements included in the 12 hour shift total 85 minutes.

All exposure levels presented in the following for individual contributing scenarios refer to working days consisting of a 12-hour shift, unless indicated otherwise.

Average hours worked per week by a 12-hour shift employee is calculated as follows:

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| **Total number of 12 hours shifts per year:** | 183 |
| **Total number of hours per year** | 2196 |
| **Hours worked per year – holiday leave entitlement (208 hours)** | 1988 |
| **Total number of 12 hours shifts per year – holiday leave entitlement considered** | 166 |

**The exposure scenario consists of 10 contributing scenarios:**

**Contributing Scenario (CS) 1 – Production process including transfers and sampling (PROC 2)**:

This CS covers the complete shift of an operative working in the production building where EDC is used. A significant portion of the 12-hour shift involves sitting in the control room or visits to the

plant production/equipment areas to undertake the following:

- Routine manufacturing activities - charging the raw materials other than EDC, QC sampling and packaging
- Visual inspections of processing plant and equipment to ensure that these are operational and no processing upsets have occurred,
- General housekeeping
- Participation in audits and investigations.

Production of Raloxifene Hydrochloride Technical material is a complex process that takes approximately 135 hours to complete from addition of EDC solvent into the reaction vessel at the start of the batch to the packaging of the Raloxifene Hydrochloride Technical into FIBCs. In order to minimise cycle times it is possible to process overlapping batches in the equipment train. Given current cycle times associated with Raloxifene Hydrochloride Technical processing, each routine production task occurs at a frequency of 48 hours. There are 10 employees in the IE8 team supporting Raloxifene Hydrochloride Technical processing, working in 4 teams (2 workers per shift), with two additional workers covering holidays, training days, etc. (when not required in the Raloxifene Hydrochloride Technical production unit these workers are deployed to another processes) (same operators as CS3 and CS4).

**Contributing Scenario (CS) 2 – Receipt of EDC from road tanker (PROC 8b)**:

This CS covers the specific operation of EDC road tanker unloading into the bulk raw solvent storage tank. This operation is done B per year by Lilly tank farm operators. Note that the actual unloading of the tanker into the raw solvent storage tank may not occur on the same 12-hour shift if the analysis of the goods receipt sample is delayed. During an unloading road tank operation, only 1 operator from tank farm area is undertaking the handling tasks. Work instruction requires a second person verification sign-off by technical support personnel of the safety critical steps. Setting up the unloading arrangement including the collection of the goods receipt sample can take approximately 30 minutes. Duration of the actual tanker unloading and subsequent disconnection of the flexible hoses is approximately 90 minutes.

The site operative with responsibility for the bulk solvent storage area also supports utilities operations. Therefore, a significant amount of the 12-hour shift is spent outside of the EDC bulk solvent storage area. There are 6 employees in the tank farm team (EC&U operators) (same operators as CS7, CS8, CS9 and CS10).

**Contributing Scenario 3 – Pre-campaign equipment preparation (PROC 8b)**:

This CS covers the sequence of tasks associated with the 'Rig Prep' activities that take place prior to the production campaign, consisting of equipment flushing with EDC and a solvent run. Initial flushing of equipment with EDC involves a series of short duration tasks (5-10 minutes each): connection/disconnection of flexible hoses; collection of solvent samples from reaction vessels (via glovebox); draining the small sections of piping which cannot be blown dry with nitrogen into portable containers. For the small sections of pipework that are not self-draining lines, potential for residual EDC is small.

For filter changes, due to QC operational reasons, it is not possible to blow EDC solvent addition lines prior to the removal of the filter. Safe operational procedures including PPE requirements are documented in the 'Rig-Prep' ticket. This operation is undertaken once per year (2 filters changed on 2 reaction vessels with a total task duration of approximately 40 minutes).

Completion of the entire sequence of pre-campaign tasks takes approximately 4.5 days (9 shifts), with a total of 190 minutes for exposure-related activities (see detailed description of tasks in 9.1). All work is carried out by IE8 operators (same operators as CS1 and CS4).

**Contributing Scenario (CS) 4 – Post-campaign maintenance and cleaning (PROC 8b)**:

This CS covers the sequence of tasks involved in the end of campaign clean-up, which takes place once per year. A clean-up involves a series of short duration tasks: connection/disconnection of flexible hoses; collection of rinse samples from reaction vessels; manual cleaning of equipment including valves. Completion of the entire sequence of tasks involved in the end of campaign clean-up takes approximately 14 days. Any potential EDC exposure is likely to occur at the beginning when parts of the system are opened (7 days assumed in section 9.1). Five personnel will be deployed to clean-up activities during a shift; this includes one IE9 Maintenance Fitter, two Contract Maintenance Fitters, two IE8 Operators (same operators as CS1 and CS3).

**Contributing Scenario (CS) 5 – Handling in laboratory work for quality control (PROC 15)**:

This CS covers the analysis of sample solutions containing EDC in the QC laboratory. Total task duration involving a GC or HPLC analytical method is approximately 4 hours, but actitvities involving potential EDC exposure are restricted to <60 min. The laboratory analyst is not involved in EDC handling tasks for the remainder of the 12-hour shift. There are six in-process quality control laboratory analysts in total. There is one analyst per shift supporting QC analysis of EDC samples and this exposure group is not the same employees as those in all other CS. If Raloxifene Hydrochloride Technical is produced in a year, 51 samples B [redacted] with an EDC content of up to 100% are analysed. In a year without a production campaign, only quarterly samples (from storage tank sampling) are analysed.

**Contributing Scenario (CS) 6 – Handling in environmental laboratory (PROC 15)**:

This CS covers the analysis of liquid waste samples (see CS9) containing EDC in the environmental laboratory. Samples taken daily are analysed batchwise once per week. Total task duration involving GC analytical methods is up to 10 hours on those days, but activities involving potential EDC exposure are restricted to the beginning and end of the work (<120 min). Samples (with EDC concentrations up to 15%) are analysed at approx. 15 days per year. The laboratory analyst is not involved in EDC handling tasks for the remainder of the 12-hour shift. There is one analyst only engaged in the analysis of waste samples and this person is not the same employees as those in all other CS.

**Contributing Scenario (CS) 7 – Sampling of stored raw solvent (PROC 8b)**:

This CS covers the sampling of EDC in storage tanks (outside) for quality control. This operation is done 4 times per year and the task takes 15 minutes to complete. The operators are not exposed to EDC for the remainder of the day shift. There are six employees in the environmental control and utilities team who support tank farm operations (EC&U operators) (same operators as CS2, CS8, CS9, and CS10).

**Contributing Scenario (CS) 8 – Filter change out on Raw Solvent Storage Tank (PROC 8b)**:

This CS covers the specific operation of changing the filter on the raw solvent storage tank. Filters are changed every twelve months. The duration is 30 minutes. This task follows site practice for a filter change-out on solvent addition lines, which requires a nitrogen purge before opening the system under a line-break permit. Filter change out instructions are outlined in a specific tank farm procedure. The tank farm operative completes this task. CS8 is covered by EC&U operators (same operators as CS2, CS7, CS9, and CS10). One operator is engaged per event.

**Contributing Scenario (CS) 9 – Waste - Collection of a liquid waste sample from the incineration feed tanks (PROC 8b)**:

Peak EDC loading of the liquid waste storage system occurs during the Raloxifene Hydrochloride Technical manufacturing campaign with typical EDC composition in the range 5-15%. In the remaining 9 months of the year when the Raloxifene Hydrochloride Technical liquid waste stream has cleared the storage system, typical EDC composition is <1%. Approx. 90 samples per year (mainly during the production campaign) are collected in 200ml septum top glass bottles from an in-line needle type sampler, which is located within a glovebox. An EC&U operator completes this task. A significant amount of the 12-hour shift of the EC&U operative is spent in the control room monitoring the operation of the waste storage tanks and the incineration units via the Distributed Control System (DCS). Occasionally the operative is required to leave the control room to conduct visual inspection of plant and equipment to ensure that these are operational and no processing upsets have occurred. CS9 is covered by EC&U operators (same operators as CS2, CS7, CS8, and CS10).

**Contributing Scenario (CS) 10 – Waste - Changing filters on the incinerator feed line (PROC 8b)**:

There is a filtration unit installed on the incinerator feed line to prevent the incinerator guns from blocking. EC&U operative is also responsible for the cleaning and operation of this unit. Equipment setup is such that it is possible to flush and purge with nitrogen prior to breaking into the system under a line break permit. Change out of the filters takes place within a glovebag. This operation is done every second week. The duration is 30 minutes (maximum). CS10 is covered by EC&U operators (same operators as CS2, CS7, CS8, and CS9). One operator is engaged per event.

**Exemption of scientific Research and Development work, including sampling and laboratory work from authorisation**

ECHA in its Q&A webpages for Q&A Reference number: ID 0585 (latest update 4 June 2015) regarding the scope of the exemption from Authorisation of activities that might be considered to be falling under scientific research and development, as per Article 56(3) laid out:

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| ***Question*** | ***"Does the exemption for the use of Annex XIV substances in scientific research and development under Article 56(3) REACH also apply to analytical activities such as monitoring and quality control?"*** |
| ***Answer*** | *"Yes, it does. Under Article 3(23) REACH, scientific research and development means any scientific experimentation, analysis or chemical research carried out under controlled conditions in a volume less than one tonne per year. Thus, scientific research and development can cover analysis, and a substance may be exempted from authorisation under Article 56(3) REACH if used, on its own or in a mixture,* ***in analytical activities such as monitoring and quality control****. For instance, routine quality control or release tests in laboratory scale using the substance as extraction solvent or analytical standard fall into the definition of "scientific research and development" under Article 3(23) REACH and in the scope of the exemption foreseen in Article 56(3) REACH, as long as the quality control or release tests are carried out under* ***controlled conditions*** *and in a volume not exceeding one tonne per year and per legal entity."* |

As this answer was ambiguous with regard to whether sampling for quality control of process chemicals used at industrial scale is included, the applicant by way of its consultants presented these questions to three national helpdesks (in UK, France and Germany) and received accordant responses to the effect that activities such as sampling and handling of substances such as EDC in a laboratory for quality control are excluded, as long as the limit of 1 ton per year is not exceeded and the substance is handled in the laboratory under "controlled conditions". The latter is not defined on an

European scale but can be interpreted as being compliant with national workplace legislation and performance of activities according to good practice (e.g., Germany's TRGS 526 "Laboratorien") (AGS, 2008). As these conditions are fulfilled, laboratory work is considered to be excluded from authorisation in this application. Nevertheless, to present a complete description of all activities involving use of EDC, information on quality control activities, along with available measurement data, are included in this report.

## 9.0.3. Overview of uses and Exposure Scenarios.

| Identifiers | Titles of exposure scenarios and the related contributing scenarios |
|---|---|
| ES1 | Exposure scenario 1:<br>Industrial use as a reaction medium and a solvating agent in mediating subsequent chemical transformation reactions leading to the manufacture of an Active Pharmaceutical Ingredient<br><br>- Industrial use of processing aids in processes and products, not becoming part of articles (ERC 4)<br>CS1 - Production process, including transfers and sampling (PROC 2).<br>CS2 - Receipt of EDC from the road tanker (PROC 8b)<br>CS3 - Pre-campaign equipment preparation (PROC 8b)<br>CS4 - End of Campaign Equipment Cleanup (PROC 8b)<br>CS5 - Handling in laboratory for quality control (PROC 15)<br>CS6 - Handling in environmental laboratory (PROC 15)<br>CS7 - Storage tank EDC sampling (PROC 8b)<br>CS8 - Filter change out on Raw Solvent Storage Tank (PROC 8b)<br>CS9 - Waste - Collection of a liquid waste sample from the incineration feed tanks (PROC 8b)<br>CS10 - Waste - Changing filters on the incinerator feed line (PROC 8b) |

## 9.0.4. Introduction to the assessment

### 9.0.4.1 Exposure-risk relationship for carcinogenic effects of EDC in humans

EDC was included in Annex XIV of REACH due to its hazard classification as a Category 1B Carcinogen. According to 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. Therefore only the human health risks related to the classification of EDC as a carcinogenic substance are addressed in this CSR.
The risks of workers exposed at their workplaces as well as the potential exposure of humans via the environment are considered.

In July 2015, ECHA published the "Reference dose response relationship for carcinogenicity of 1,2-dichloroethane" as endorsed by RAC. The following table summarises the recommendations, which will be used for risk characterisation in this report.

**Table 10. Exposure-risk relationships for 1,2-dichloroethane as recommended by RAC (ECHA, 2015)**

| Population | Pathway | Risk estimate | Concentration/dose at risk level |
|---|---|---|---|
| Workers | Inhalation | $6.0 \times 10^{-7}$ per µg/m$^3$ | 16.7 µg/m$^3$ corresp. to $1 \times 10^{-5}$ |
| | Dermal | $2.1 \times 10^{-6}$ per µg/kg bw/day | 4.8 µg/kg bw/day corresp. to $1 \times 10^{-5}$ |
| General population | Inhalation | $3.45 \times 10^{-6}$ per µg/m$^3$ | 0.29 µg/m$^3$ corresp. to $1 \times 10^{-6}$ |
| | oral | $1.2 \times 10^{-5}$ per µg/kg bw/day | 0.083 µg/kg bw/day corresp. to $1 \times 10^{-6}$ |

The risk estimate for dermal exposure of workers was derived by RAC assuming 50% percutaneous

absorption. As in this chemical safety report, dermal exposure is calculated by estimating the amount absorbed through skin by applying a model using the flux rate (see sections 5.1, 9.0.4.2 and Appendix 4) (and hence the absorbed dermal dose is obtained), a risk estimate per dose twice of that in the table above is used: $4.2 \times 10^{-6}$ per µg/kg bw/day (absorbed dose).

All other values are used for the risk characterisation in this report as given in the table.

### 9.0.4.2 Workers

#### 9.0.4.2.1 Inhalation exposure assessment

**Contributing Scenarios 1 and 2** (CS1 Production process, including storage, transfers, sampling, waste transfers, CS2 Receipt of EDC from road tank)

For the two main contributing scenarios covering the production process (CS1) and road tank unloading (CS2), measured data are available. Two measurement campaigns were carried out in 2014/2015. Measurements were performed according to (further details are given in Appendix 1):

- CSN EN 689 "Workplace atmospheres – Guidance for the assessment of exposure by inhalation to chemical agents for comparison with limit values and measurement strategy"
- BOHS (2011) Testing Compliance with Occupational Exposure Limits for Airborne Substances
- ECHA guidance R.14, 2012
- ISO 16200 (NIOSH 1003) "Workplace air quality -- Sampling and analysis of volatile organic compounds by solvent desorption/gas chromatography".

Similar Exposure Group (SEG) exposed to EDC have been identified across the plant site and linked with the Contributing Scenarios. The sample collection technique used was personal air sampling (the sampling device is placed in the worker's breathing zone). A clear description of all technical conditions and tasks completed during the sampling duration was provided to the analytical laboratory. As per NIOSH requirements a certified laboratory was selected for the analysis of the personal air samples.

EDC is used in a closed system with high levels of engineering control and well defined working processes. Potential exposure during production campaigns are expected to be very low. Historical exposure assessment data are available, but are not representive of current conditions, as technical improvements regarding sampling were implemented in previous years. Sampling now takes place in a glovebox, essentially reducing exposure to a minimum.

**Contributing Scenarios 3 and 4** (Pre- and post-campaign activities)

No exposure measurements are available for these activities, which are tasks carried out during short time periods before and after the annual production campaign. Due to the infrequent nature of these tasks and the limited window of opportunity to capture them, it was difficult to plan and carry out measurement campaigns and to achieve sufficient values for an assessment. Therefore, tier 2 modelling using Advanced REACH Tool (ART, v1.5) was used for inhalation exposure assessment. Only employees who are trained and essential to carry out these specific tasks are permitted to work in areas where these activties take place. Whilst emergency maintenance and repair operations are the most un-predictable, procedural controls are in place to minimise exposure to workers and the environment. Regardless of when or where maintenance activities occur, safe entry/breaking into process lines, service pipes, pumps and equipment requires a 'Line Breaking and Lock Out Permit'. At a minimum the permit dictates that piping must be flushed and then blown dry with nitrogen where possible. If cleaning and maintenance activities require the employee to enter a piece of equipment a 'Confined Space Entry Permit' is required. PPE requirements are included in both of these permits.

**Contributing Scenarios 5 and 6** (Laboratory work)

For CS5 and CS6, again tier 2 modelling with Advanced REACH Tool was used as the main assessment approach. Measured data from 2015 campaign (2 measurements) are available for the quality control laboratory to support the assessment.

**Contributing Scenario 7, 8, 9 and 10** (Activities related to maintenance tasks and waste operations)

As for CS3 and CS4 above, these are tasks carried out infrequently and are difficult to plan for. As no exposure measurements exist, the exposure assessment is based on tier 2 modelling with ART.

**Time and frequency of exposure at workplaces**

The dose-response relationship for EDC recommended by RAC for workers assumes a life-time exposure of 8 hours per day, 240 days per year during a working life of 40 years. Lilly operates a 24-hour rotating shift schedule, with employees working 2 consecutive days with 12-hour day shifts (08:00-20:00) followed by 2 consecutive days with 12-hour night shifts (20:00-08:00), followed by 4 days off.

When calculating excess cancer risks the following correction is made:

Based on 4 working days followed by 4 rest days, the working time is 15 shifts/month or 166 shifts per year. As detailed above, the working hours per year for workers in 12 hour shifts are 1988 hours (including 85 minutes for breaks per shift). Working hours in typical 8-hour shifts are: 8 hours x 240 work days per year: 1920 hours per year
For long-term exposures it can therefore be assumed that total working time is similar for 8-hour and for 12-hour shifts (i.e. 3 months in 12-hour shifts compare to 3 months in 8-hour shifts).

For calculating excess cancer risks for short-term activities, the total yearly working time will be divided by 1920 hours (or the numbers of 12-hour shifts per year will be divided by 166) to compare the obtained yearly average exposure with ECHA's dose-response relationship.

**Respiratory protection equipment**

When RPE is used during a task, the following efficiencies are assumed to calculate the actual exposure (Howie (2005)):

- 95% efficiency: Full face cartridge respirators with filters ABEK (combination filter Organic Vapour/Acid Gas/ Ammonia/ Dust/Mist Cartridge, A2 B2 E2 K2-P3) conforming with EN136, which is used by the tank farm operators (CS2, CS7, CS8).
- 90% efficiency: disposable half-face cartridge respirator; used in the production building for pre-campaign activities and maintenance and cleaning tasks involving potential EDC exposure (CS3, CS4, CS10) (in areas directly involved in the handling of highly potent API the policy is to use disposable PPE to minimise contamination issues).

Specific PPE are selected and approved by the site EHS department. Employees are provided with individual items of PPE, which are available in designated storage areas. Employees receive training and qualitative and quantitative face fit testing as appropriate priorto using any item of RPE. The filters of the full face masks are changed after each use (the efficiency values are based on British Standards Institution, London, 1997, American National Standards Institute, New York, 1992 and ART TNO report 2009).

RPE is worn only during specific periods/for specific activities (e.g. sampling and disconnecting

hoses during tank truck unloading). Estimation of a full-shift exposure estimate (or 12 hour TWA exposure concentration) taking into consideration the protection provided by the RPE worn for specified tasks during a shift is calculated as follows:

$$C_{real} = \frac{[(Conc.\ A * Time\ A \times 0.05) + (Conc.\ B * Time\ B \times 0.05) + \ldots\ldots (Conc.\ N * Time\ N \times 0.05)\ ] + (Conc._{noRPE} * Time_{noRPE})}{(Time_{RPE} + Time_{noRPE})}$$

Where:
**$C_{real}$** TWA (time weighted average) 12 hour exposure estimate
**Conc. A, B ….N** Measured concentration of tasks A, B ….N when RPE is worn
**Time A, B ….N** Time duration in minutes for tasks A, B ….N
**0.05** Protection factor provided by the respirator worn
**Conc. $_{noRPE}$** Measured concentration of a task or partial shift (mg/m$^3$) when RPE is not worn[1]
**Time $_{noRPE}$** Task or partial shift duration (minutes) when RPE is not worn
**1**

As part of the measurement study personnel wear both full-shift and task specific samples. Since a full shift sample for workers in CS2 includes time periods with and without RPE, **Conc.$_{noRPE}$** is calculated as follows:

$$Conc._{noRPE} = \frac{(Conc._{Full\text{-}shift} * Time_{Full\text{-}shift}) - [(Conc.\ A * Time\ A \times 0.05) + (Conc.\ B * Time\ B \times 0.05) + \ldots\ldots (Conc.\ N * Time\ N \times 0.05)\ ]}{(Time_{full\text{-}shift} - Time_{noRPE})}$$

Where:
**Conc. $_{Full\text{-}shift}$** Shift related concentration (mg/m$^3$)
**Time$_{Full\text{-}shift}$** Total duration of full-shift in minutes
**Time$_{noRPE}$** Duration of full-shift in which no RPE is worn

### 9.0.4.2.2 Dermal exposure assessment

#### General considerations

EDC is handled only by experienced and specifically trained workers who are also instructed in preventing any dermal contact, e.g. through splashes of the substance. Furthermore, due to its eye and skin irritating effect, risk management measures are in place to minimise dermal exposure. Workers wear gloves during all tasks involving a potential release of EDC to prevent exposure due to unforeseen events. All of these measures are implemented to minimise the risk of dermal exposure.

Apart from these use- and site-specific considerations, EDC is a highly volatile substance with vapour pressures of 8130 Pa at 20 °C and 10247 Pa at 25 °C (see section 1.3). This chemical property may lead to significant evaporation losses, which reduces the amount of EDC potentially available for dermal absorption (see e.g. Frasch et al., 2014; Kissel, 2011). This fact is also acknowledged in the ECHA Guidance on occupational exposure estimation (ECHA, 2012b), which proposes considering the evaporation time in relation to dermal absorption and refers to an equation for calculation of the evaporation (see Appendix R.14-1 in ECHA (2012b)).

#### Dermal Exposure Modelling

Several tools are available for modelling dermal exposure. The standard tier 1 tool under REACH (ECETOC TRA) as well as the more advanced RISKOFDERM model (both discussed in ECHA (2012b)) do not specifically address the high volatility of substances such as EDC and do not include a term accounting for evaporation from the skin (or from gloves).

Use of RISKOFDERM for dermal exposure assessment was considered, but disregarded for this assessment, due to following reasons:

- RISKOFDERM was developed for substances and situations with significant dermal exposures; therefore choices for input parameters available in the model are not easily related to the exposure situations described in this report.
- Scenarios (so-called dermal exposure operation (DEO) units), available in RISKOFDERM do not cover all activities relevant here; especially, handling of contaminated objects was excluded from DEO unit 1 in the latest version of the model (v2.1), as explained in the model's "Changes and validity" spreadsheet. This missing activity is especially relevant for handling objects during maintenance activities.
- RISKOFDERM was not intended for modelling involving highly volatile substances, nor are datasets including such substances part of the empirical database used to establish the model. The draft version of the revised ECHA Guidance on Information Requirements and CSA, R.14, Occupational Exposure Assessment, (draft version of November 2015) states for RISKOFDERM that "*Due to a lack of data on dermal exposure to volatile substances, the model is not optimally suitable for very volatile substances (e.g. > 500 Pa vapour pressure). Use with input values outside those found in the measured data sets should be avoided, though results may still be indicative."*
- Considering the high volatility of EDC, dermal exposure assessment with RISKOFDERM would require setting the time to volatilisation equal to the exposure duration in the model, the justification of which is unclear; furthermore, the volatilisation times calculated for EDC for the activities here (see below and in Appendix 4) are below the range of applicable exposure durations of the model.

In conclusion, RISKOFDERM was not considered suitable for the exposure situations in this report and a methodology was established, which is based on consideration of evaporation of highly volatile substances according to ECHA (2012b).

One tool that does address evaporation from the skin and compares it with dermal absorption is the 'Finite Dose Skin Permeation Calculator' (http://www.cdc.gov/niosh/topics/skin/finiteSkinPermCalc.html), a model that has been developed for the U.S. National Institute for Occupational Safety and health (NIOSH). The model is described in detail in the literature (Fedorowicz et al., 2011; Kasting and Miller, 2006; Kasting et al., 2008; Miller and Kasting, 2010; Wang et al., 2007). However, recent evaluations by Gajjar (Gajjar, 2010; Gajjar and Kasting, 2014) have shown that this model may underpredict dermal absorption of EDC.

In the light of these considerations, the evaporation time of EDC was first calculated according to the ECHA Guidance (see Appendix R.14-1 in ECHA (2012b)). Based on these data, two methods for estimating dermal exposure were implemented. The overall approach is described below and full details are included in Appendix 4.

**Calculation of the evaporation time**

For the assessment of dermal exposure in the context of this CSR, the evaporation time was calculated according to the equation in Appendix R.14-1 in ECHA (2012b) with the following modifications:

- Use of an EDC-specific mass transfer coefficient (11.6 m/h), rather than using the default value (8.7 m/h) in ECHA (2012b).

- Calculation of the evaporation time for dermal loads (0.1-1.0 mg/cm$^2$), rather than 1 and 5 mg/cm$^2$ in ECHA (2012b)[6]. These loads reflect default dermal exposure for PROCs relevant for the use evaluated here (i.e. PROC 2, 8b, and 15).

Full details of input parameters and results of this calculation are included in Appendix 4. The evaporation times calculated are:

- **0.94 seconds** for a dermal load of **0.1 mg/cm$^2$** (applicable e.g. to PROC15 according to ECETOC TRA (ECETOC, 2004; 2009; 2012).
- **1.9 seconds** for a dermal load of **0.2 mg/cm$^2$** (applicable to PROC2 according to ECETOC TRA (ECETOC, 2004; 2009; 2012).
- **9.4 seconds** for a dermal load of **1 mg/cm$^2$** (applicable to PROC8b according to ECETOC TRA (ECETOC, 2004; 2009; 2012).

These represent conservative estimates, since (a) a vapour pressure at 20 °C was applied, which represents a conservative estimate for evaporation from skin and (b) a low value for the air velocity was applied in calculating the mass transfer coefficient that has a high impact on the estimate. The upper end of air velocities typical for occupational settings according to the ECHA Guidance (ECHA, 2012b) would result in lower evaporation times of 0.59 - 5.9 seconds for the dermal loads of 0.1-1 mg/cm$^2$.

The evaporation times calculated cover situations relevant in the context of this CSR, i.e. when splashes or small amounts of EDC are deposited on gloves. Full immersion of the hands in EDC is not covered, since evaporation may not be a relevant process for dermal exposure in these situations.

The evaporation times calculated were used in two different approaches: (a) Approach 1 using contact area, evaporation time and dermal flux; (b) Approach 2 using contact surface area and glove permeation rate.

Both approaches, which are discussed in detail in Appendix 4, result in very similar estimates of dermal exposure per event as shown in Table 11.

**Table 11. Estimation of dermal exposure: summary***

| **Parameter** | **Unit** | **PROC** | | |
|---|---|---|---|---|
| | | **2** | **8b** | **15** |
| Dermal dose per event (*potential*) – **approach 1** | µg/kg | 0.13 | 1.3 | 0.033 |
| Dermal dose per event (*actual*) – **approach 1** | µg/kg | 0.0066 | 0.066 | 0.0017 |
| Dermal dose per event (actual) – **approach 2** | µg/kg | 0.0043 | 0.043 | 0.0011 |

* Actual exposure estimates include the protection offered by gloves (95% efficiency assumed for approach 1 estimates). All values rounded to two significant figures, but unrounded values were taken for calculation.

The above estimates are critically dependent on the skin surface area that was conservatively chosen based on ECETOC TRA defaults for the PROCs indicated in Table 11. The PROCs are also related to default dermal loads of 0.1 (PROC 15), 0.2 (PROC 2) and 1 mg/cm$^2$ (PROC 8b) that have an impact on the evaporation time calculated (see above). However, no modelling with ECETOC TRA was involved in these calculations and the doses estimated would equally apply to PROCs with identical contact areas and loads (or, in fact, to tasks for which these contact areas and loads could be verified).

Both approaches have advantages and disadvantages, as fully discussed in Appendix 4. For the

[6] In the model calculations (Table R.14-17 of the Guidance), these values are described as amounts (1 mg and 5 mg) and no contact area is given (although required in the equation). Re-calculations for toluene, however, show that these values actually refer to loads in mg/cm$^2$.

purpose of dermal exposure assessment, the higher estimates of Approach 1 will be used. Both estimates already include the protection offered by wearing suitable gloves (actual dermal exposure).

The dermal exposure estimates presented in Table 11 are event-based, since rapid evaporation is assumed for each event. However, some tasks may be performed several times a day. As a consequence, the number of events has to be taken into account. This will be addressed in each worker contributing scenario in section 9.1, for which dermal exposure is estimated. Similarly, exposure may not occur on a daily basis (e.g. for maintenance tasks). Again, the exposure frequency is task-specific and will be addressed in each worker contributing scenario in section 9.1.

The following matrix illustrates the calculation used for each relevant worker contributing scenario in Section 9.1 (where only one PROC applies).

**Table 12. Matrix for calculating task-specific dermal exposures (example activity)**

| **Parameter** | **Unit** | **PROC 2** | **PROC 8b** | **PROC 15** |
|---|---|---|---|---|
| Dermal dose per event (potential), product | µg/kg | 0.13 | 1.3 | 0.033 |
| Number of events per day | 1/d | 10 | | |
| Dermal dose per day (potential), product | µg/(kg x d) | 1.3 | | |
| Concentration of EDC in product | % | 100% | | |
| Dermal EDC exposure (potential) | µg/(kg x d) | 1.3 | | |
| Efficiency of PPE (gloves) | % | 95 | | |
| **Dermal EDC exposure (actual)** | **µg/(kg x d)** | **0.066** | | |

* All values rounded to two significant figures, but unrounded values were taken for calculation.

When dermal protection equipment (gloves) is used, an efficiency of 95% is used to calculate the actual exposure. The 95% efficiency can be justified by the use of protective gloves satisfying the specifications of EU Directive 89/686/EEC and the associated standard EN 374. Specific training is given to all workers handling EDC and using PPE(see above).

**Table 13. Table Permeation Data for Gloves Associated with CS2 - CS8**

| **CS** | **Material** | **Thickness** | **Breakthrough Time** |
|---|---|---|---|
| CS2, CS3, CS4, CS7 & CS8 | Neoprene | 0.66 mm | 8 minutes |
| CS5 | Nitrile | 0.12 mm | 3 minutes |
| CS6 | Nitrile | 0.15 mm | suitable for splash contact* |

* information provided by glove supplier: nitrile gloves suitable for single splash exposure to EDC (inhouse tested by short-term immersions in solvent). Not suitable for immersion

As only splash contact to EDC is possible at the workplaces and after a careful hazard assessment carried out by the plants' occupational safety department, glove materials with breakthrough times of 3 to 8 minutes were considered sufficient, Contaminated gloves are not allowed to be reused.

#### 9.0.4.2.3 General information on risk management related to irritation classification

EDC is classified for its irritating properties. The applicant is a downstream user of EDC. Operational conditions and risk management measures, as communicated by the supplier in the safety data sheet for this use, are closely followed to avoid any detrimental effects such as irritation of skin, eyes or the respiratory tract.

### 9.0.4.3. Exposure of humans via the environment

The assessment is based on measured concentrations in emitted air and waste water, which are used to calculate site-specific release factors. These release factors are used as input data for modelling with EUSES (European Union System for the Evaluation of Substances) (v.2.1.2).

Site specific EDC consumption information is used to calculate the release factors. Whereas detailed information on trends is given in the Analysis of Alternatives report, the following estimates for 2015 are used here, based on the volume of EDC consumed in 2013 (B tonnes/year).

For the assessment, an average release scenario was developed that assumes continuous use of EDC (365 days per year). While in reality, EDC is used in batch operations on 90 consecutive days per year, this approach was chosen since the monitoring values from which release factors were calculated cover periods of both EDC use and non-use. The average release scenario is also appropriate in this case, since the assessment addresses a chronic effect (carcinogenicity) and the exposure estimated is assumed to exist over an entire lifetime (assumed to be 75 years (ECHA, 2015)).

However, a separate intermittent release scenario was also modelled. This scenario assumes the highest releases to air and water (as obtained from the monitoring data) occur on 90 days per year (the actual days of EDC use at the site). By default, the concentrations in air and other media will then be averaged over the year in EUSES. It is therefore expected that this approach leads to similar values. However, a separate model was run to exclude any unforeseen differences (e.g. concentration levels in media that are not linearily related to the release).

#### 9.0.4.3.1 Substance-specific input data

The following data were used as input in EUSES modelling. A Koc of 33 L/kg and a BCF of 2 in fish for EDC was reported in OECD (2002; these values are also cited in section 4 of this CSR). However, the EUSES default values for EDC (calculated from log Kow) are used in the assessment (Koc = 59.4 L/kg, BCF fish = 3.41 L/kg w.wt.), since (a) the data reported in OECD (2002) are not well documented and (b) the differences are small.

**Table 14. Physico-chemical data, environmental properties and environmental partition coefficients used as input values in EUSES (see chapter 1.3)**

| End points | Values |
|---|---|
| Molecular weight | 98.96 g/mol |
| Melting point | -36 °C |
| Boiling point | 83.6 °C |
| Vapour pressure at 25°C | 10247 Pa |
| Octanol-water partition coefficient (log Kow) | 1.45 |
| Water solubility at 25°C | 7900 mg/l |

The ECHA Guidance on consumer exposure estimation (ECHA, 2012c) recommends a default body weight of humans of 60 kg, while EUSES employs a default body weight of 70 kg. The body weight in EUSES is used for estimating the intake of a substance from food. The underlying food consumption data are based on the highest country-average consumption rate for each food product. As noted by the developers of EUSES, this "*will of course lead to a total food basket, which is an unrealistic, worst-case scenario*" (RIVM, 2004). Since EUSES therefore assumes a very high intake of food, the default body weight of EUSES was used in the assessment.

**9.0.4.3.2 Releases to air**

***Waste air:***
All process gas vents are connected (closed system) to the production building scrubber caustic units. After the scrubber unit, the off gas is transferred to the fume incineration unit operated at 850 $^{o}$C. HCl releases after incineration are treated by scrubber tower. Post-scrubber stack gas emissions are continuously monitored for HCl and volatile organic compounds (VOCs) as per license requirements.

Speciated VOCs analysis of the stack gas emission is carried out on a monthly basis as per license requirement. EDC concentrations measured are given below. (Emission data from 2013 are used as this year was the last one providing a typical production schedule – in 2014, an unscheduled plant shutdown occurred, caused by events unrelated to Raloxifene Hydrochloride production). EDC was measured by GC-MS (thermal desorption) (sampling time 30 min, Limit of Quantification (LOQ) 0.03 mg/m$^3$).

**Table 15. EDC air emissions measured in 2013**

| **Date** | **Air flow (m$^3$/day)** | **Concentration (mg/m$^3$)** |
|---|---|---|
| 21/01/2013 | 13438 | 0.11 |
| 01/02/2013 | 3244 | 0.10 |
| 04/03/2013 | 11172 | 0.06 |
| 05/04/2013 | 14281 | 0.05 |
| 09/05/2013 | 11173 | 0.03 |
| 12/06/2013 | 15484 | 0.10 |
| 04/07/2013 | 13601 | 0.10 |
| 09/08/2013 | 12472 | 0.10 |
| 09/09/2013 | 12106 | 0.06 |
| 03/10/2013 | 28265 | 0.17 |
| 01/11/2013 | 26685 | 0.03 |
| 04/12/2013 | 16521 | 0.16 |
| **Arithmetic mean** | **14870** | **0.09** |

The arithmetic mean values are used for determining site-specific release rates. With a total release of **1.34 g EDC/d** or 488.5 g EDC/year (0.09 mg/m$^3$ x 14870 m$^3$/d x 365 d/year) and the tonnage of EDC used at the site as given above a release rate to air of B [redacted] results.

***Fugitive/diffuse emissions:***

**Solvent storage tank:**
Solvent storage tank breathing and working losses is the main contributor to such emissions.
Technical measures in place to minimise emissions are:

- A material of construction assessment ensures that all equipment and piping is compatible with the hazardous chemicals handled or stored in any application.
- High integrity valve packing and seals are installed on transfer piping.
- Maximal use is made of the automated process control system to ensure that manual intervention is minimal.
- All external storage tanks are located in bunded areas, which are designed to contain 110% of the tank volume. An integrity test programme ensures that all bunds are tested on a regular basis.

- A centrifugal pump with mechanical seal is used to complete the transfer from the road tanker into the storage tank.
- The EDC storage vessel is a pressure rated single walled tank with nitrogen padding system in place. The tank materials of construction are 316L stainless steel to minimise the risk of corrosion.
- Tank venting arragements - conservation vent set at 200 mBarg to carbon adsorber abatement system and 500 mBarg emergency vent to atmosphere.
- The storage tank is installed with level controls incorporating a level transmitter and high level switch. The high level alarm and high-high level alarms switch activation are independent alarms. The activation of the high level switch and the automated fill inlet valve are interlocked, independent of the high level alarm.
- A centrifugal pump with mechanical seal is used to complete the transfer to the production facility via fixed piping.

Working losses occur primarily from tank filling operations. Based on typical volumes of EDC used on-site it is estimated that previously this led to a combined breathing and working tank loss for both pure EDC storage and EDC present in waste tanks, of approximately 80 kg per annum. This value is based on USEPA (United States Environment Protection Agency) methodology for calculation of fugitive emissions in Guidance AP42 (1) Section 7.1 Organic Liquid Storage Tanks.

In order to further eliminate these fugitive emissions, in September 2015 a carbon absorber unit was installed to capture emissions from the EDC raw solvent storage tank (see Figure 2, Appendix 6), while piping all off gases from the waste solvent storage tanks to the existing fume incinerator. Given that the carbon absorber has a removal efficiency of at least 99% and the fume incinerator has a removal efficiency of 99.2% with the new technique installed the expected overall annual emission of EDC from these fugitive sources is reduced to less than 1kg.

Diffuse emissions from other tanks and installations are minimised by the following means:

**IE8 Reaction Vessels and Mother liquor tanks:**

- All reaction and mother liquor treatment vessels are glass lined, pressure rated double walled tanks.
- All reaction vessels are connected to the site fume duct so that all gasous emissions undergo destruction in the site fume incinerator.
- Enclosed transfers between vessels via fixed piping and pressure rated contained process hoses.
- Low emission pumps with mechanical seals e.g. centrifugal or air operated diaphragm pumps are used.
- In case of an emergency all production floor drainage can be collected in a bunded waste tank adjacent to the building thus minimising the risk of an uncontained release.

**Waste Storage Tanks:**

- Liquid waste storage vessels are pressure rated single walled tanks with nitrogen padding system in place. The tank materials of construction are carbon steel to minimise the risk of corrosion.
- Tank venting arrangements - Conservation vent is routed to the fume incineration unit to prevent release of fugitive emissions to atmosphere as level rises in the tank.

- Enclosed transfers between vessels via fixed piping and pressure rated contained process hoses.
- Low emission pumps with mechanical seals i.e. centrifugal are used to complete transfers between vessels.
- Storage tanks are installed with level controls incorporating a level transmitter and high level switch. The high level alarm and high-high level alarms switch activation are independent alarms. The activation of the high level switch and all inlet/outlet valves are interlocked, independent of the high level alarm.

In the production building (IE8) where EDC processing takes place, routine monitoring is also carried out on fugitive/diffuse emissions from the building ventilation exhaust. In 2013, no EDC was detected in any of the samples collected from the ventilation exhaust system (LoQ 0.1 mg/$m^3$). This provides confirmation of the effectiveness of the containment measures in place for each of the EDC processing steps within the building.

***Ambient Air monitoring***

Ambient air monitoring for speciated VOCs is carried out at a station downwind of the site (at a distance of ca. 500 meters). Sampling is by passive means onto absorbent tubes which are collected on a monthly basis and submitted to a specialised air analysis laboratory. Sampling and analysis is undertaken by independent third party. There was no evidence of EDC above 0.05 ppb (quantification limit of analytical method) in any ambient air samples collected in 2013 and 2014 (absorption on Tenax diffusion tubes, analysis with GC/MS). This provides further verification of the effectiveness of the control measures in place for EDC containment across the site.

**Waste solvent treatment**

All waste solvent from storage tanks are transferred by closed lines to an on-site incinerator unit. This incinerator is operated and controlled under license in accordance with the conditions outlined in the Industrial Emissions Directive (2010/75/EU). The unit operates at 1150 °C with a two second residence time. The incinerator achieves a destruction efficiency of at least 99.999%.

The incinerator gas cleaning equipment consists of a two-stage process comprised of a condenser/absorber for acid gas removal and a hydrosonic scrubber for particulate and droplet removal. Incinerator stack gases are continuously monitored for a range of parameters including Hydrocarbons and HCl with all data recorded in a validated continuous emissions monitoring system. Hydrocarbon emissions from the incinerator are well within the daily average emission limit values as outlined in the Industrial Emissions Directive (2010/75/EU).

**9.0.4.3.3 Releases to water**

All process waste waters (EDC concentration in waste water streams is very low <0.1 µg/L) are collected in storage vessels and pumped via a closed loop to the wastewater treatment plant (WWTP) for biological degradation. The WWTP can provide up to 2200 $m^3$ aeration capacity in a conventionally operated activated sludge plant. Also, the WWTP also incorporates the treatment of liquid effluent from the incinerator gas cleaning process through a combination of a clarifier and sand filter solids removal unit.

Sludges from the WWTP are mixed, dewatered and sent offsite to a licenced sludge drying facility before being forward processed for use as a fuel substitute in the cement manufacturing industry or equivalent. Thereby ensuring complete destruction of any residual EDC absorbed in the sludge.

All off gases from the WWTP are collected from the roofed tanks (balance tank, aeration tanks and sludge digestion tanks) and routed to the Biofilter. The Biofilter has a capacity of greater than 190,000 $Nm^3$/day air flow, sufficient to service both the aeration basins and the sludge holding

tanks. While the primary function of the Biofilter is odour abatement, it additionally supports residual VOC removal. Analysis of both the Biofilter inlet and outlet gas streams has demonstrated a >99% removal efficiency for EDC with discharge concentration less that the limit of quantification of the test method.

Treated effluent from both the biological WWTP and the incinerator sand filter are gathered in a final holding tank prior to discharge to the sea. Flow proportional composite sampling is carried out on the final effluent discharge with analysis conducted for a range of parameters as outlined in the current Industrial Emission License. Included in this monitoring is monthly analysis for EDC concentrations in the final effluent. Analysis results are given below. Values from 2013 are used for the assessment for the same reasons as given above. EDC is analysed by Purge/Trap-GC-MS, with a LoQ of 0.1 µg/L

**Table 16. EDC concentrations in WWTP effluent measured in 2013**

| **Date** | **Effluent volumes ($m^3$/day)** | **Concentration (µg/L)** |
|---|---|---|
| 17/01/2013 | 1189 | <0.1 |
| 07/02/2013 | 1004 | <0.1 |
| 11/03/2013 | 1162 | <0.1 |
| 05/04/2013 | 946 | <0.1 |
| 07/05/2013 | 1228 | <0.1 |
| 24/06/2013 | 1195 | 1.9 |
| 11/07/2013 | 1310 | 0.4 |
| 26/08/2013 | 1067 | 0.5 |
| 19/09/2013 | 996 | 1.8 |
| 14/10/2013 | 877 | 0.4 |
| 20/11/2013 | 1282 | <0.1 |
| **Arithmetic mean** | **1114** | **0.48 *** |

* values below LOQ were taken as 0.5 * LOQ

The arithmetic mean values are used for determining site-specific release rates. With a total release of **0.535 g EDC/day** or 195 g EDC/year (0.48 µg/L x 1114 $m^3$/d x 365 days/year) and the tonnage of EDC used at the site as given above a release rate to water of B [redacted] results.

While EUSES requires some adaptation of the release factors used as input data[7], note that the assessment is based on monitoring data obtained in the effluent prior to discharge into the water compartment. Since such measurements are independent of assumptions on the behaviour of a substance during waste water treatment (in contrast e.g. to measurements in process streams before waste water treatment), the ultimate release estimated is considered very reliable.

As outlined in the introduction to this section, apart from the average release scenario (for which the input parameters are presented above), an intermittent release scenario was run as well. This intermittent release scenario applies maximum releases to air and water on 90 day per year (true number of EDC use) instead of 365 day per year in the average long-term scenario. For this purpose, releases were calculated for each monitoring day for releases to air and the maximum value for releases to water .

For the intermittent release scenario, the following releases were derived (based on the highest EDC concentrations observed in 2013 in air and WWTP effluent):

[7] The release factor given refers to the release in the effluent before entering the water compartment (i.e. after the WWTP). EUSES requires release factors from the process, i.e. before waste water treatment. Since 47.7 % of the substance is assumed to be released to the river in EUSES, the release factor from the process is higher than the value given in the text. For EUSES modelling, the release factor after waste water treatment was divided by 0.477 and the resulting (higher) release factor was used. This is entirely a technical issue for EUSES modelling. The modelled concentration in the effluent (after waste water treatment) is identical to the monitored values that were used as the basis in deriving release factors.

- Release to air: 4.81 g/day on 90 days/year (instead of 1.34 g/d on 365 days/year)
- Release to water: 2.27 g/day on 90 days/year (instead of 0.535 g/d on 365 days/year)

The individual releases for 2013 and the values derived for the average release and intermittent release scenario are plotted in the following figure.

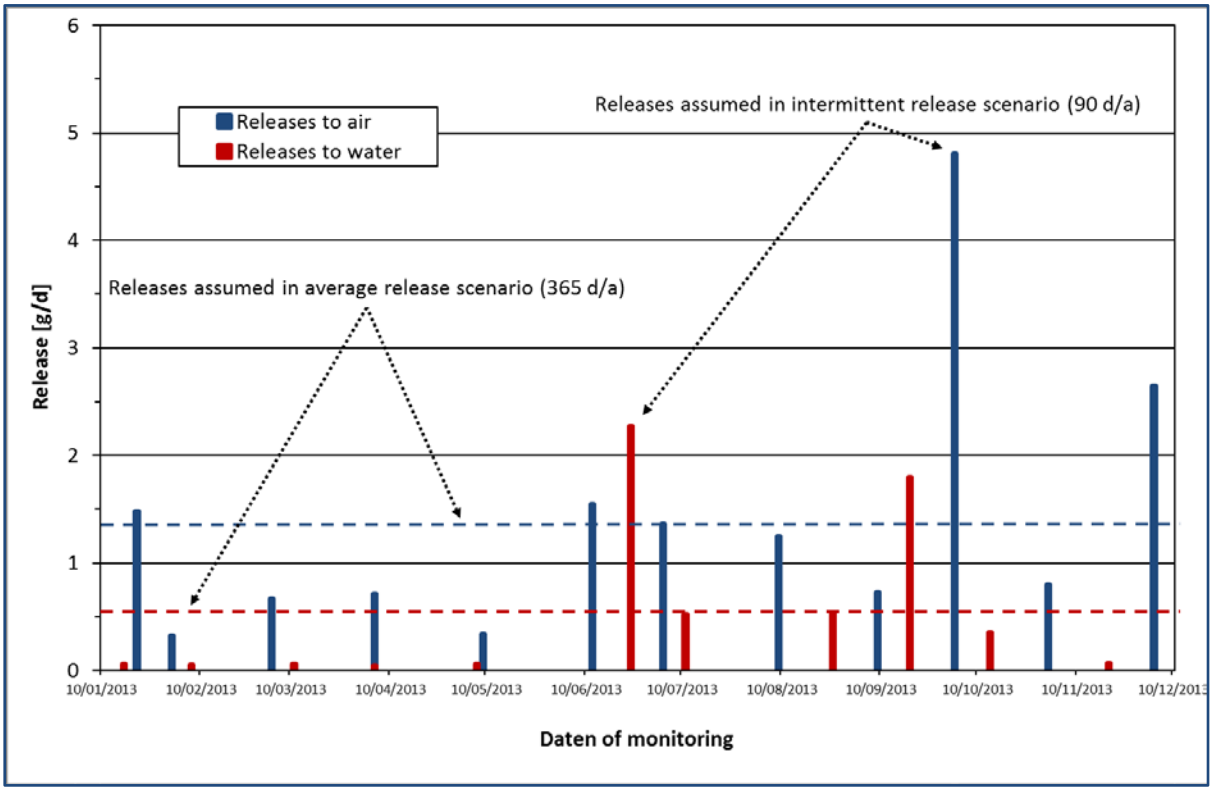


Figure 2: Releases of EDC to air and water: individual values and releases used for the average release and the intermittent release scenario

**Additional input values**

The WWTP effluent from the site is not discharged to freshwater, but is collected in a holding tank and then discharged into the sea. EUSES does not allow such a differentiated assessment and assumes direct releases to both freshwater and marine water. This approach would predict EDC concentrations in freshwater that would be taken as the basis for EDC concentrations in drinking water. Since this discharge situation does not exist at the site, the freshwater dilution factor was set to 1000, resulting in very low EDC concentrations in this compartment. Note that this approach will result in EDC concentrations in freshwater (into which no EDC is released) that also have an impact on the concentration (e.g. in fish used in EUSES to calculate oral intake).

The default dilution factor for the marine environment is 100. Dilution and dispersion around the site's outfall in Kinsale has been the subject of research for the last 35 years (for matters unrelated to EDC). Most recently, dilution and dispersion was modelled by Kennedy (2012) to check compliance with EU environmental objectives[8]. This exercise was based on very conservative assumptions led to a minimum dilution of 2080 at 200 m from the outfall. On the basis of these data, the dilution factor

[8] Kennedy, R.: Near field dilution and dispersion model of the Eli Lilly outfall, Kinsale Harbour, in relation to EC Environmental Objectives (Surface Waters) Regulations (S.I. No. 272/2009). Submitted to Eli Lilly S.A., Dunderrow, Co. Cork, Ireland by Dr Robert Kennedy, Marine Ecosystem Research Laboratory, Zoology, Ryan Institute, School of Natural Sciences, National University of Ireland, Galway, Galway, Ireland, 31 May 2012

for the marine environment was set to 2000 in EUSES modelling.

No substance is released to soil from the production unit. No sludge is applied to soil and the default dry sludge application rate for agricultural soil and grassland in EUSES was set to zero.

**Soil and groundwater monitoring**

Further evidence regarding on-site containment of EDC comes from the results of soil and groundwater monitoring activities.

A soil survey was completed in 2014 as part of a Baseline Report for a license review application under the Industrial Emissions Directive. Sampling locations were in close proximity to potential high risk activities i.e. production building, raw solvent storage tanks and liquid waste storage tanks. A detailed suite of solvent analyses (VOC, semivolatile organic compounds (SVOCs), Alcohol/Acetate) was conducted on all soil samples collected with results indicating that all solvents in the suite, including EDC, were below the limit of detection (LOD) for the test method. The LOD for EDC is 4 ug/L in this instance.

Groundwater monitoring is conducted on a bi-annual basis on a number of monitoring wells across the site as required by license. Again a detailed suite (VOC, SVOC, Alcohol/Acetate) of analyses was conducted on these samples with no evidence of EDC present in the groundwater at the limit of quantitation of the test method (0.1 ug/L) in analyses from recent years.

These results reaffirm the site's commitment to maintaining good operational practices and controls around the handling of hazardous substances including EDC.

### 9.0.4.3.4 Mass Balance Considerations

EDC is handled in a closed system throughout the plant and therefore few fugitive emissions are expected. This is corroborated by the low occupational exposure levels measured during production, low emissions detected by routine monitoring of ventilation exhaust of production building (IE8) and low concentrations measured during ambient air monitoring (see above for details). The trace levels of EDC measured in effluent discharge also corroborate the containment measures in place. In the past the EDC raw solvent storage tank might have been a source for some emissions to air, but with the installation of carbon absorber unit in September 2015 this potential emission source has been eliminated. Potential EDC emissions from the waste solvent storage tanks have also been eliminated by the collection of these tank vents and routing of off gases to the fume incinerator.

The use of EDC occurs in a multi-process facility, requiring waste solvent from all processes to be collected in large volume static storage tanks prior to destruction by incineration. Solvent constituents of the liquid waste mixture are immiscible so 'layering' will occur in the tank, making it almost impossible to quantify EDC content within each static storage tank. If accumulations of each constituent within the tank cannot be measured accurately, relatively small errors in estimations and assumptions can lead to large errors in the overall EDC calculation. As this represents a large portion of any mass balance calculation the completion of an accurate EDC mass balance in these circumstances is not considered feasible. Therefore it is considered more appropriate to focus efforts on the environmental monitoring programme in place, which demonstrates that potential impacts from releases to air and water of EDC are insignificant. This monitoring programme, which covers all pathways is summarised in Table 17 that follows.

**Table 17. Summary of Environmental Monitoring Programme**

| Monitoring Type | Parameters(s) | Frequency | Analysis Method |
|---|---|---|---|
| ***Releases to Air*** | | | |
| Stack Gas Emissions – Fume Incineration Unit | HCL and VOC | Continuous | IR (infra-red) and FID (flame ionisation detection) |
| Stack Gas Emissions – Fume Incineration Unit | EDC | Monthly | GC-MS (thermal desorption) |
| Stack Gas Emissions – Liquid Waste Incineration Unit | HCL and VOC | Continuous | IR and FID |
| Working & Breathing losses from storage tanks | Specific VOCs including EDC | Annual | Emissions modelling (USEPA Guidance AP42 (1) Section 7.1 Organic Liquid Storage Tanks) |
| Building Ventilation Fans | EDC | Bimonthly | Adsorption tube (GC-MS) |
| Ambient Air Monitoring – Off-site Location | EDC | Monthly | Tenax diffusion tubes GC-MS (thermal desorption) |
| ***Waste Solvent Treatment*** | | | |
| Primary Liquid Waste Stream prior to Incineration | EDC | Daily | GC-FID (flame ionisation detection) |
| Secondary Liquid Waste Stream prior to Incineration | EDC | Daily | GC-FID (flame ionisation detection) |
| ***Releases to Water*** | | | |
| Treated WWTP effluent in final holding tank | EDC | Monthly | Purge & Trap (GC-MS) |
| ***Soil and Ground Water*** | | | |
| Soil survey | EDC | 5 yearly | Headspace (GC-MS) |
| Ground water monitoring | EDC | Bi-annual | Purge & Trap (GC-MS) |

# 9.1 Exposure scenario 1: Industrial use as a reaction medium and a solvating agent in mediating subsequent chemical transformation reactions leading to the manufacture of an Active Pharmaceutical Ingredient, Raloxifene Hydrochloride

## 9.1.1. Environmental contributing scenario: Use as process and extracting solvent in fine chemical processes

As EDC is listed in REACH Annex XIV due to its carcinogenic effects, no environmental exposure assessment is performed here. However, human exposure via the environment is addressed.

### 9.1.1.1 Conditions of use

**Table 18. Conditions of use for the Kinsale site**

| **Amount used, frequency and duration of use (or from service life)** |
|---|
| • Daily use at site: B [redacted] (amount not recovered and used for exposure assessment) |
| • Annual use at a site: B [redacted] (amount not recovered and used for exposure assessment) |
| • Emission days: 90 days/year (batch operation) |
| **Conditions and measures related to sewage treatment plant** |
| • Industrial STP: Yes |
| • Discharge rate of STP: 1114 $m^3$/day |
| • Application of the STP sludge on agricultural soil: no |
| **Other conditions affecting environmental exposure** |
| • Receiving surface water flow rate: not applicable (discharges to marine environment)<br>• Dilution factor (marine environment): 2 000 (site-specific, see section 9.0.4.3) |

### 9.1.1.2. Releases

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

**Table 19. Local releases to the environment***

| **Release** | **Release factor estimation method** | **Explanation / Justification** |
|---|---|---|
| **Water** | Measured release (Site-specific data) | **Final release factor:** B [redacted] (after on-site treatment)<br>**Local release rate:** 0.535 g/day (after on-site treatment)<br>**Justification:** see section 9.0.4.3 |
| **Air** | Measured release (Site-specific data) | **Final release factor:** B [redacted]<br>**Local release rate:** 1.34 g/day<br>**Justification:** see section 9.0.4.3 |
| **Soil** | Release factor (Site-specific data) | **Final release factor:** 0% |

* The data reported refer to the average release scenario that forms the basis for this assessment (see section 9.0.5.3 for details and justification)

### 9.1.1.3. Exposure and risks for human exposure via the environment

The modelled EDC concentrations for inhalation exposure and EDC doses for oral exposure are reported in the following tables for both the regional and the local scale (average release scenario). The full EUSES report is included in Appendix 5 of this CSR.

**Table 20. Modelled exposure for humans via the environment: inhalation**

| | **EDC concentration [µg/m$^3$]*** |
|---|---|
| Regional PEC in air | 2.15E-07 |
| Local PEC in air | 3.73E-04 |

PEC Predicted Air Concentration

These EDC concentrations were modelled under the assumption of average releases over the entire year (average release scenario). If maximum releases on 90 days per year are assumed (intermittent release scenario, see section 9.0.4.3 for details and justification), regional and local PECs (defined as annual averages) are similar (96 % and 88 % of the values shown in the table above for the regional and local scale, respectively).

**Table 21. Modelled exposure for humans via the environment: oral**

| **Scale** | **EDC oral intake [µg/(kg x d)]** |
|---|---|
| Regional assessment | 2.19E-08 |
| Local assessment | 2.50E-05 |

All values rounded to three significant figures for presentation, but unrounded values were used for calculation of sums

Again, the EDC exposure levels shown are based on average releases over the entire year (average release scenario). If maximum releases on 90 days per year are assumed (intermittent release scenario, see section 9.0.4.3 for details and justification), the exposure levels are similar (104 % and 92 % of the values shown in the table above for the regional and local scale, respectively).

All exposure estimates are based on release factors that were in turn calculated from measured data. The finding that the intermittent release scenario leads to similar exposure estimates (in fact, it leads to slightly lower estimates in three of the four estimates) confirms the approach taken in the main assessment (average release scenario).

The oral exposure estimates are dominated by intake via drinking water (about 67 % of total oral intake in both the local and the regional assessment). In the present case, the EDC concentration in drinking water is derived from the EDC concentration in groundwater. It is worth noting that the modelled EDC concentration in groundwater is simply derived in EUSES by setting the concentration in soil porewater as equal to the concentration in groundwater (RIVM, 2004). These authors state that "*this is a worst-case assumption, neglecting transformation and dilution in deeper soil layers*" (RIVM, 2004). In addition, the concentration in soil porewater is driven by deposition of EDC from the air. Such deposition is modelled in the EUSES local assessment for a circle around the source with a radius of 1000 m, which can be considered another conservative assumption. Finally, no mixing with other water is assumed in EUSES when equating the concentration in groundwater with the concentration in drinking water. Despite these conservative assumptions, the modelled concentration in drinking water (0.000595 µg/L) is more than three orders of magnitude lower than the limit value of 3 µg/L according to Council Directive 98/83/EC, which, according to WHO (2003) corresponds to a risk of 1 x $10^{-6}$.

Groundwater from the on-site wells have repeatedly been shown to be below the analytical LoQ (<0.1 µg/L; see section 9.0.4.3).

The exposure estimated is multiplied with the exposure-risk relationship for carcinogenic effects of EDC in the general population (see section 9.0.4.1). The following table shows the resulting risks for both the regional and the local scale. The risks are presented for each of the two relevant pathways as well as for total exposure (risks for inhalation and oral exposure added).

**Table 22. Risk estimates for humans via the environment**

| Scale | Inhalation exposure | Oral exposure | Total exposure |
|---|---|---|---|
| Regional assessment | 7.42E-13 | 2.63E-13 | 1.00E-12 |
| Local assessment | 1.29E-09 | 3.00E-10 | 1.59E-09 |

The calculated risks in the regional assessment are extremely low and are at least six orders of magnitude lower than the "indicative tolerable risk level" of $10^{-6}$ for the general population (ECHA, 2012a). In the local assessment, the risk from total exposure is almost three orders of magnitude lower than this "indicative tolerable risk level" and is dominated by the contribution of inhalation exposure (81% of total exposure).

This risk estimate for local inhalation exposure has to be put into perspective. In EUSES, the local PEC in air is modelled for a point 100 meters from the source, a distance "*assumed to be representative for the average size of an industrial site*" (RIVM, 2004).

The site is a large production facility located in a rural area. No residential or commercial properties are to be found within a 100m radius from any of the following potential emission sources:

- Road tanker unloading bay
- Raw solvent storage tank
- Production building where chemical synthesis takes place
- Waste storage tanks and incineration units.

Eli Lilly has knowledge of the number of properties that fall within a radius of 1000m from the site boundary, as a result of Seveso directive obligations. 81 properties can be found within this range.

In addition, the concentration in air and the deposition (a key determinant for the concentration in groundwater) are estimated in EUSES with the Operational Priority Substances (OPS) model that is embedded in EUSES. When EUSES was developed, conservative input values were chosen (e.g. stack height of 10 m, no excess heat of the plume emitted compared to environmental temperature and an ideal point source). The developers of the OPS model at the Dutch National Institute for Public Health (RIVM) more recently analysed the impact of these conservative default settings on the estimated concentration in air and on the total deposition. These authors concluded that '*air concentration and total deposition used for risk assessment purposes are likely to be overestimated due to over-conservative default settings used in the standard scenario in EUSES*' (de Bruin et al., 2010). In light of these findings, the risk estimates presented above are highly conservative.

**Conclusions**

In summary, the risks calculated are very low. The total risk for the local assessment is dominated by inhalation exposure (81 %) and oral exposure via dinking water from groundwater (13 %), together accounting for 94 % of the total local risk estimated. For reasons outlined above, risk estimates for both pathways are considered very conservative. The total risk calculated for the local assessment is therefore even more conservative.

## 9.1.2. Worker contributing scenario 1: Production process, including transfers, sampling, waste transfers (PROC 2)

As described in the introduction of chapter 9.0, production of the pharmaceutical active substance using EDC occurs in closed systems without direct handling of EDC by operators.
The CS1 covers all phases of the production process, during which EDC is used or transferred via closed lines.

### 9.1.2.1. Conditions of use

| |
|---|
| **Product characteristics** |
| • 1,2-dichloroethane – liquid |
| **Amount used, frequency and duration of use/exposure** |
| • The industrial site is producing in a batch process, 24/24, for approx. 90 days). |
| **Technical and organisational conditions and measures** |
| • All equipment in the production units involving use of EDC are closed systems. Sampling is via gloveboxes. |
| • Local exhaust ventilation: none |
| **Conditions and measures related to personal protection, hygiene and health evaluation** |
| • Dermal Protection: no |
| • Respiratory Protection: no |
| **Other conditions affecting workers exposure** |
| • Place of use: Indoor – good general ventilation |

### 9.1.2.2. Exposure and risks for workers

Raloxifene Hydrochloride is produced in campaigns of 3 months duration (currently one campaign per year). The CS1 (PROC2) is covering full shift operations (12 hours). Activities carried out by operators:

A significant portion of the 12-hour shift involves sitting in the control room.
Activities in production building IE8 comprise the following:

- Routine manufacturing activities - charging the raw materials other than EDC, QC sampling and packaging
- Visual inspections of processing plant and equipment to ensure that these are operational and no processing upsets have occurred, general housekeeping
- Participation in audits and investigations.
- Routine sampling for quality control via glovebox.

**Inhalation exposure assessment**

Two measurement campaigns were carried out (in December 2014/January 2015 and November 2015), delivering 11 long-term measurements for IE8 Operators engaged in CS1. All but one value were below the LoQ. Therefore, the resulting $90^{th}$ percentile value from this set of data is close to this single measured value. The $90^{th}$ percentile value of 0.08 $mg/m^3$ is used for risk calculations. The arithmetic mean is 0.026 $mg/m^3$ (which is approximately half of the LoQ). The data and the statistical evaluation are presented in detail in Appendix 2.

**Dermal exposure assessment**

Potential dermal exposure with EDC may only occurr during sampling for quality controls. As sampling is done using a glovebox, no dermal exposure is expected for CS1 (see description in chapter 9.0 and Figure 8, Appendix 6).

**Exposure and risk estimate**

**Table 23. Exposure concentrations and risks for workers (CS1)**

| Route of exposure | TWA 12 h exposure concentration | Correction factor for frequency | corrected long-term exposure concentration | Excess cancer risk |
|---|---|---|---|---|
| Inhalation | 0.080 mg/m$^3$ | Frequency: 0.25* | 0.02 mg/m$^3$ | 1.2 x 10$^{-5}$ |
| Dermal | - | - | - | not applicable |
| Combined routes | | | | 1.2 x 10$^{-5}$ |

** Frequency: activity takes place 3 months/year (production campaign); correction factor = 0.25*

*No other correction for comparing TWA results for 12h shifts to ECHA's dose-response relationship is required here, because average exposure duration of workers per month is similar for 12h and 8h shifts (see 9.0.4.2).*

Exposure levels are low and derived from one single long-term measurement which found a concentration above the LoQ.

## 9.1.3. Worker contributing scenario 2: Receipt of EDC from road tanker (PROC 8b)

### 9.1.3.1. Conditions of use

EDC (liquid) is supplied by road tanker, each delivery contains approximately 27,000 litres of solvent. On average there are B road tanker deliveries per year to support the production campaign.

After goods receipt document checks are completed by security personnel the delivery driver moves the road tanker to the designated unloading bay. Inventory mangement documentation and safety checks are then undertaken by the tank farm operative.

Connection of a pressurised supply of nitrogen to the road tanker during the unloading process, use of flexible hoses with dry lock couplings and a pumped transfer ensures that this operation occurs within a closed system (see Figure 1, Appendix 6). The manway on the top of the roadtanker remains closed. The unloading task is covered by work instructions which require second person verification signoff to cover the safety critical steps (in particular the attachment of an earth monitoring unit clamp to the road tanker and the nitrogen connection tasks).

Collection of a goods receipt sample is via a sampling device attachment, which is connected to the bottom outlet valve on the road tanker. A 300ml clear glass bottle is attached to the sampling device via a screw-in connection. The operative collects the sample in accordance with the sampling protocol which outlines the PPE requirements for the task - disposable coveralls, neoprene gloves, full face respirator with an appropriate cartridge.

After confirmation of goods receipt sample approval from the QC laboratory, the transfer of the contents of the road tanker into the raw solvent storage tank begins, which takes approximately 90

minutes. During this time the operative can leave the tanker unloading bay returning perdiodically to check the tanker. The tank receiving level can be monitored remotely from a nearby control room. When the road tanker is empty, the system is flushed with nitrogen before the hoses are disconnected and placed on a designated storage rack.

| |
|---|
| **Product characteristics** |
| • 1,2-dichloroethane – liquid |
| **Amount used, frequency and duration of use/exposure** |
| • B per year, 90 minutes. |
| **Technical and organisational conditions and measures** |
| • Transfer via closed lines |
| • Local exhaust ventilation: none |
| **Conditions and measures related to personal protection, hygiene and health evaluation** |
| • Dermal Protection: yes, during sampling and connecting/disconnecting hoses (effectiveness: 95%) |
| • Respiratory Protection: yes, during sampling and connecting/disconnecting hoses (effectiveness: 95%) |
| **Other conditions affecting workers exposure** |
| • Place of use: outdoor |

### 9.1.3.2. Exposure and risks for workers

CS2 covers the specific operation of EDC road tanker unloading into the bulk raw solvent storage tank. This operation is performed B per year by Lilly tank farm operators. Note that the actual unloading of the tanker into the raw solvent storage tank may not occur on the same 12-hour shift if the analysis of the goods receipt sample is delayed. During an unloading road tank operation, only 1 operator from the tank farm area is doing the handling tasks. Work instruction requires a second person verification sign-off by the area supervisor of the safety critical steps. Setting up the unloading arrangement including the collection of the goods receipt sample can take approximately 30 minutes. Duration of the actual tanker unloading and subsequent disconnection of the flexible hoses is approximately 90 minutes.

**Inhalation exposure assessment**

Two measurement campaigns were carried out (in December 2014/January 2015 and October 2015), delivering 10 long-term measurements for EC&U Operators engaged in CS2. Periods during which operators wore respiratory protection (sampling and connecting/disconnecting hoses, efficiency 95%) were sampled in parallel with a second sampling pump. This allows considering the impact of wearing respiratory protection during these short-term activities on the shift average. The detailed equations used are given in section 9.0.4.2.1 and in Appendix 2, where all data and the statistical evaluation are presented in detail.
An arithmetic mean of 0.33 mg/m$^3$ and a 90$^{th}$ percentile of 1.77 mg/m$^3$ for shift averages result from these data. The 90$^{th}$ percentile is used for risk calculations.

**Dermal exposure assessment**

As described above there are 3 main phases during the unloading operation: sampling, connecting/disconnecting flexible hoses and unloading. No dermal exposure is expected during the unloading phase as the operator is only performing visual control. During sampling and disconnecting the hose exposure to liquid EDC is possible. One splash during sampling and one during disconnecting the hose is assumed.

The procedure to estimate dermal exposure to EDC and to consider evaporation of the substance is described in 9.0.6.2.2 and Appendix 4.

**Table 24. Task-specific dermal exposure assessment**

| **Parameter** | **Unit** | **PROC 8b** |
|---|---|---|
| Dermal dose per event (potential), product | µg/kg | 1.33 |
| Number of events per day | 1/d | 2 |
| Dermal dose per day (potential), product | µg/(kg x d) | 2.65 |
| Concentration of EDC in product | % | 100 |
| Dermal EDC exposure, (potential) | µg/(kg x d) | 2.65 |
| Efficiency of PPE (gloves) | % | 95 |
| **Dermal EDC exposure (actual)** | **µg/(kg x d)** | **0.13** |

* All values rounded to two significant figures, but unrounded values were taken for calculation.

**Exposure and risk estimate**

**Table 25. Exposure concentrations and risks for workers (CS2)**

| Route of exposure | TWA 12 h exposure concentration | Correction factor for frequency | corrected long-term exposure concentration (group average) | Excess cancer risk |
|---|---|---|---|---|
| Inhalation | 1.77 mg/m$^3$ | 0.007* | 0.012 mg/m$^3$ | 7.4 x 10$^{-6}$ |
| Dermal | 0.13 µg/(kg x d)** | 0.007* | 0.00093 µg/(kg x d) | 3.9 x 10$^{-9}$ |
| Combined routes | | | | 7.4 x 10$^{-6}$ |

** Frequency: activity takes place* B [redacted] *per year (166 d); as only* B [redacted] *is required per event (plus one supervisor) the average frequency is* B [redacted] *= 0.007*

*** RPE and gloves used during sampling and connecting/disconnecting hoses: 95% efficiency for both inhalation and dermal exposure*

Due to low exposure levels and a low frequency of the activity, the resulting calculated risks are low. Dermal exposure is negligible compared to the contribution by inhalation.

## 9.1.4. Worker contributing scenario 3: Pre-campaign equipment preparation (PROC 8b).

### 9.1.4.1. Conditions of use

CS3 covers the sequence of tasks associated with the 'Rig Prep' activities that take place prior to the production campaign (4.5 days per year). Initial flushing of equipment with EDC ("Wet end EDC flushing") is followed by the "Solvent run" period.

After the EDC flush the system is emptied and purged with nitrogen. Following this a series of short duration tasks (5-10 minutes each) are carried out. Tasks in relation to EDC flushing are the

following: connection/disconnection of flexible hoses, collection of solvent samples from reaction vessels via glovebox (negligible exposure), and draining small sections of piping, which cannot be blown dry with nitrogen, into portable containers. For the small sections of pipework that are not self draining lines, potential residual EDC volumes are small (<200ml per section). Completion of the entire sequence of tasks involved in the emptying of the equipment train with EDC and the following purging with nitrogen and opening the system takes approximately 36 hours. After this phase the "Solvent Run" phase follows, lasting 3 days. This essentially is a 'dummy run' of the production process using only the raw solvents to test the batch recipe on the Distributed Control System. Here, exposure-relevant activities are draining pipes and changing two filter cartridges.

As during production, sampling occurs via gloveboxes and is assumed not to result in any significant exposure. The most relevant activities are opening lines by disconnecting hoses, draining EDC from low points, and changing filters after the solvent run. These activities were modelled with the ART, using the following conservative task durationss:

- disconnecting hoses (3 x, during Wet end EDC flushing): 30 min
- draining EDC from low points: 160 min (total aggregated duration during "Wet end EDC flushing" (10 x) and "Solvent Run" (4 x))
- changing filter cartridges (twice during "Solvent Run" period): 40 min

These are the total times required for carrying out all tasks during one pre-campaign phase. These tasks are done by several workers.

| **Product characteristics** |
|---|
| • 1,2-dichloroethane – liquid, neat substance |
| **Amount used, frequency and duration of use/exposure** |
| • 4.5 days per year |
| **Technical and organisational conditions and measures** |
| • Size of filter cartridges: <1 $m^2$ (0.4 – 0.6 $m^2$)<br>• Size of openings of small hoses: <1 $m^2$<br>• Total volumes of EDC drained during both phases: <10 L |
| • Local exhaust ventilation: none |
| **Conditions and measures related to personal protection, hygiene and health evaluation** |
| • Dermal Protection: yes (effectiveness: 95%) |
| • Respiratory Protection: yes (effectiveness: 90%) |
| **Other conditions affecting workers exposure** |
| • Place of use: Indoor – good general ventilation |

### 9.1.4.2. Exposure and risks for workers

**Inhalation exposure assessment**

As no monitoring data are available, exposure modelling using ART (V1.5) was used (see all ART protocols in Appendix 3). In short, conditions used for the various activities modelled were:

- Activity 1: disconnecting hoses after purging with nitrogen: 50 to 90% EDC in the residual liquid, surfaces < 1 $m^2$, surface contamination 10 – 90%, duration 30 min
- Activity 2: draining low points: neat EDC, volumes <10 L, duration 160 min,
- Activity 3: changing filter cartridges: 50 to 90% EDC in the residual liquid, surfaces < 1 $m^2$, surface contamination 10 – 90%, duration 40 min.

Despite purging with nitrogen, a conservative assumption was made that most of the surfaces are covered by liquid.

In the modelling these tasks are included in one shift, although actually they are distributed over 9 shifts during the pre-campaign period. One operator out of the group of 10 IE8 operators is involved per task which means that not all operators are exposed. Average exposure levels are calculated below from the ART results.

As ART is set to assume 8-hours shifts, in ART 8/12 of real exposure durations are used to obtain the same ratio of exposed versus non-exposed periods for the 12 hours shifts worked by IE8 operators.

- for disconnecting hoses: 30 min * 8/12 = 20 min
- for draining low points: 160 min * 8/12 = 107 min
- for changing filter cartridges: 40 min * 8/12 = 27 min

An exposure estimate of 200 mg/m$^3$ (result without PPE efficiency considered; upper limit of inter-quartile confidence interval to the 75th percentile; the 90$^{th}$ percentile amounts to 170 mg/m$^3$) is obtained with ART under the assumption that all tasks are carried out within one shift (see Appendix 3). Actually, as explained above, these short-duration tasks are carried out over a period of 4.5 days or 9 12-hour shifts, with two operators per shift, which results in 18 operator shifts. Therefore, the shift average is 11.1 mg/m$^3$. The estimated shift-average exposure considering RPE efficiency of 90% is **1.1 mg/m$^3$**.

**Dermal exposure assessment**

Based on a task analysis the following number of events per task is assumed:

- disconnecting hoses (total duration 30 minutes): 10 splashes
- draining EDC from low points of lines (total duration 160 minutes): 30 splashes
- changing filter cartridges (total duration 40 minutes): 10 splashes

In consequence, it is assumed that during all pre-campaign activities a total of 50 splashes may occur, where liquid contents (neat EDC) from equipment drop on an operator's gloves.

The procedure to estimate dermal exposure to EDC and to consider evaporation of the substance is described in Section 9.0.4.2.2 and Appendix 4.

**Table 26. Task-specific dermal exposure assessment**

| **Parameter** | **Unit** | **PROC 8b** |
|---|---|---|
| Dermal dose per event (potential), product | µg/kg | 1,33 |
| Number of events per day | 1/d | 50 |
| Dermal dose per day (potential), product | µg/(kg x d) | 66.3 |
| Concentration of EDC in product | % | 100 |
| Dermal EDC exposure, (potential) | µg/(kg x d) | 66.3 |
| Efficiency of PPE (gloves) | % | 95% |
| **Dermal EDC exposure (actual)** | **µg/(kg x d)** | **3.3** |

* All values rounded to two significant figures, but unrounded values were taken for calculation.

**Exposure and risk estimate**

**Table 27. Exposure concentrations and risks for workers (CS3)**

| Route of exposure | TWA 12 h exposure concentration | Correction factor for frequency | corrected long-term exposure concentration | Excess cancer risk |
|---|---|---|---|---|
| Inhalation | 1.1 mg/$m^3$ ** | 0.011* | 0.012mg/$m^3$ | 7.3 x $10^{-6}$ |
| Dermal | 3.3 µg/(kg x d)** | 0.011* | 0.036 µg/(kg x d) | 1.5 x $10^{-7}$ |
| Combined routes | | | | 7.5 x $10^{-6}$ |

** Frequency: 10 IE8 operators are engaged in CS3 tasks: 2 operators are active in each of the 9 shifts = correction factor: 18 shifts/10 operators: 1.8 shift per operator; 1.8/166 shifts = 0.011*

*** RPE and gloves used during exposure-related activities (90 and 95% efficiency, resp.)*

## 9.1.5. Worker contributing scenario 4: End of campaign equipment cleanup (PROC 8b)

CS4 addresses annual maintenance activities after termination of the production campaign.

### 9.1.5.1. Conditions of use

Manufacturing equipment cleaning takes place at the end of each campaign. Therefore, the frequency of these activities is once per year. Special procedures for the end of campaign cleanup including flushing instructions and PPE requirements are documented in the 'turnaround' ticket. Tanks and pipework including valves are flushed with A% [redacted] solution in water and is then blown dry with nitrogen before opening under a line-break permit. Whilst the clean-in-place system is very effective at cleaning the internal surfaces of the reaction vessels, valves must be taken apart so that component parts can be manually cleaned.

| |
|---|
| **Product characteristics** |
| • 1,2-dichloroethane – liquid, minute concentration |
| **Amount used, frequency and duration of use/exposure** |
| • two weeks per year (first week relevant for exposure) |
| **Technical and organisational conditions and measures** |
| • inside |
| **Conditions and measures related to personal protection, hygiene and health evaluation** |
| • Dermal Protection: yes (effectiveness: 95%)<br>• Respiratory Protection: yes (effectiveness: 90%) |

### 9.1.5.2. Exposure and risks for workers

CS4 covers the sequence of tasks involved in the end of campaign cleanup which takes place once per year. A cleanup involves a series of short duration tasks: connection/disconnection of flexible hoses; collection of rinse samples from reaction vessels; and manual cleaning of equipment including valves. Completion of the entire sequence of tasks involved in the end of campaign cleanup takes approximately 14 days. However, minimal EDC exposure is expected to occur midway through this 14 day period when equipment is opened after a methanol solution flush. Five personnel are deployed to cleanup activities during a shift including a IE9 Maintenance Fitter, two Contract Maintenance Fitters and two IE8 Operators.

**Inhalation exposure assessment**

As there is no existing measurement data regarding maintenance operations, a tier 2 model assessment approach using ART was used (see all details of ART inputs in Appendix 3):
In a conservative approach an exposure duration of ¾ of a full shift was assumed, whereas in practice short periods of exposure-related activities alternate with many other activities. As ART is set to assume 8-hours shifts, exposure duration of 6 hours was assumed and the shift average concentration obtained was used as shift average for the 12-hours shift at Lilly. This equates to assuming ¾ * 12 hours = 9 hours of exposure during a 12-hours shift.
ART input parameters:

- Activity 1 = maintenance – duration 360 mins (No exposure period = 120 mins) (see above)
  EDC concentration 0.01 to 0.1%: Before any dismantlement, the equipment is extensively flushed with A% [redacted] solution and purged and blown dry with nitrogen; therefore, potential residual EDC will be minute.
  For maintenance operations it is assumed that emission source is located in the breathing zone of the worker. The relevant activity description from ART for maintenance is handling of contaminated objects with surface 1 - 3 $m^2$ (opening of valves, hose connections etc., most objects have much smaller surface areas) with a contamination of 10 to 90 % of surface (e.g. opening equipment for vessel inspection, conservative assumption, in face of nitrogen purging).

Workers wear RPE (half-masks) and gloves during all exposure-related tasks.

An exposure estimate of 1.8 mg/$m^3$ (result without PPE efficiency; upper limit of inter-quartile confidence interval to the 75th percentile;the 90$^{th}$ percentile amounts to 1.5 mg/$m^3$) is obtained with ART (see Appendix 3). The exposure result (shift average concentration) considering PPE efficiency of 90% is **0.18 mg/$m^3$**.

**Dermal exposure assessment**

It is assumed that during one shift of routine maintenance activity up to 20 splashes may occur, where liquid contents from equipment drop on the gloves. Again, in agreement with ART assumptions, it is assumed that the concentration of EDC (after flushing and purging) is <0.1%.

The procedure to estimate dermal EDC exposure and to consider evaporation of the substance is described in Section 9.0.4.2.2 and Appendix 4.

**Table 28. Task-specific dermal exposure assessment**

| **Parameter** | **Unit** | **PROC 8b** |
|---|---|---|
| Dermal dose per event (potential), product | µg/kg | 1.3 |
| Number of events per day | 1/d | 20 |
| Dermal dose per day (potential), product | µg/(kg x d) | 26.5 |
| Concentration of EDC in product | % | 0.1 |
| Dermal EDC exposure, (potential) | µg/(kg x d) | 0.027 |
| Efficiency of PPE (gloves) | % | 95 |
| **Dermal EDC exposure (actual)** | **µg/(kg x d)** | **0.0013** |

* All values rounded to two significant figures, but unrounded values were taken for calculation.

**Exposure and risk estimate**

**Table 29. Exposure concentrations and risks for workers (CS4)**

| Route of exposure | TWA 12 h exposure concentration | Correction factor for frequency | corrected long-term exposure concentration | Excess cancer risk |
|---|---|---|---|---|
| Inhalation | 0.18 mg/m$^3$ ** | 0.02* | 0.0036 mg/m$^3$ | 2.2 x 10$^{-6}$ |
| Dermal | 0.0013 µg/(kg x d)** | 0.02* | 0.000026 µg/(kg x d) | 1.1 x 10$^{-10}$ |
| Combined routes | | | | 2.2 x 10$^{-6}$ |

** Frequency: exposure period: 1 week per year; company workers work in 12 h shifts, contract maintenance workers in 8 h shifts: an average working time per week of 40 hours is assumed; correction factor = 40/1988=0.02. Only 2 out of the group of 10 IE8 Operators are involved (not considered here).*

*** RPE and gloves used during exposure-related activities (90 and 95% efficiency, resp.)*

Again, dermal exposure is negligible compared to inhalation exposure.

## 9.1.6. Worker contributing scenario 5: Laboratory quality control (PROC 15)

### 9.1.6.1. Conditions of use

The 'in-process' laboratory analyst is responsible for the analysis of raw solvent and reaction completeness samples which takes place in designated fumehoods within the laboratory (see Figure 9, Appendix 6). Transfer of material from the sample bottle into smaller vials for analysis is conducted within the fumehood. Open handling of chemicals on laboratory benches is not permitted. The HVAC system serving the laboratory has a dedicated air handling unit so that there is 100% fresh air supply with approx. 30 air exchanges per hour. Exhaust air from the fumehoods is not re-circulated, it is HEPA filtered prior to discharge to the atmosphere.
When all tests are complete, surplus sample material is disposed of in the sample sink which is piped into the liquid waste system. The empty sample bottle and cap is placed in a waste drum for incineration.

| **Product characteristics** |
|---|
| • 1,2-dichloroethane – liquid |
| **Amount used, frequency and duration of use/exposure** |
| • 51 samples per year |
| **Technical and organisational conditions and measures** |
| • Local exhaust ventilation: fume cupboard |
| **Conditions and measures related to personal protection, hygiene and health evaluation** |
| • Dermal Protection: yes (effectiveness: 95%) |
| • Respiratory Protection: none |
| **Other conditions affecting workers exposure** |
| • Place of use: Indoor – 30 ACH |

### 9.1.6.2. Exposure and risks for workers

CS5 covers the analysis of samples containing EDC in the QC laboratory. If Raloxifene Hydrochloride Technical is produced in a year, 51 samples B [redacted] with an EDC content of up to 100% are handled in the laboratory per year. Total task duration involving GC or HPLC analysis of one sample is approximately 4 hours, but handling of EDC under the fumehood is restricted to a much shorter time period (assumed to be 1 hour). The remainder of the time is dedicated to GC runs etc. The laboratory analysts are not exposed to EDC for the remainder of the 12-hour shift. There are six quality control laboratory analysts involved in the analysis of EDC-containing sample material (not involved in other CSs). Only one person works with one individual sample

**Inhalation exposure assessment**

Only a few measurements are available for exposure during performing laboratory activities including EDC-containing samples. Therefore, exposure was modelled using the tier 2 ART. ART input parameters (see Appendix 3):

- Activity 1 = laboratory – duration 40 mins (No exposure period = 440 mins) (40 min duration was chosen, as ART assumes 8 hour shifts; the calculated average concentration for 40 min/8 hours is equivalent to an exposure duration of 1 hour per 12 hour-shift)
  Activity model: transfer of falling liquids, flow <0.1 l/min which is adequate for transfers of small volumes in the laboratory (sample flask < 500 ml). Splash loading in an open process was chosen as worst case. Fume cupboards are used for all EDC handling. ACH 30 is assumed. At least some of the samples may contain neat EDC, therefore a concentration of 100% is assumed.

An exposure estimate of **0.16 mg/m$^3$** (upper limit of inter-quartile confidence interval to the 75th percentile; the 90$^{th}$ percentile amounts to 0.14 mg/m$^3$) is obtained with ART (see Appendix 3).

Two personal sampling long-term measurements were performed with two laboratory staff members handling EDC samples in December 2014 and January 2015 respectively. Both results were below the LOQ of 3 µg (<0.288 mg/m$^3$ and <0.183 mg/m$^3$, respectively). These mesurements support the results from ART modelling.

**Dermal exposure assessment**

It is assumed that during one shift (1 hour) up to 8 splashes may occur, where liquid contents from samples drop on the gloves.
The procedure to estimate dermal exposure to EDC and to consider evaporation of the substance is described in Section 9.0.4.2.2 and Appendix 4.

**Table 30. Task-specific dermal exposure assessment**

| **Parameter** | **Unit** | **PROC 15** |
|---|---|---|
| Dermal dose per event (potential), product | µg/kg | 0.033 |
| Number of events per day | 1/d | 8 |
| Dermal dose per day (potential), product | µg/(kg x d) | 0.265 |
| Concentration of EDC in product | % | 100% |
| Dermal EDC exposure, (potential) | µg/(kg x d) | 0.265 |
| Efficiency of PPE (gloves) | % | 95% |
| **Dermal EDC exposure (actual)** | **µg/(kg x d)** | **0.013** |

* All values rounded to two significant figures, but unrounded values were taken for calculation.

**Exposure and risk estimate**

**Table 31. Exposure concentrations and risks for workers (CS5)**

| Route of exposure | TWA 12 h exposure concentration | Correction factor for frequency | corrected long-term exposure concentration | Excess cancer risk |
|---|---|---|---|---|
| Inhalation | 0.16 mg/$m^3$ | 0.05* | 0.008 mg/$m^3$ | 4.8 x $10^{-6}$ |
| Dermal | 0,013 µg/(kg x d)** | 0.05* | 0.0007 µg/(kg x d) | 2.8 x $10^{-9}$ |
| Combined routes | | | | 4.8 x $10^{-6}$ |

** Frequency: 51 samples are handled per year, an individual sample is handled by one laboratory worker only: correction factor: 51 samples/166 shifts * 1/6 staff members = 0.05*

*** Gloves are used during exposure-related activities (95% efficiency)*

## 9.1.7. Worker contributing scenario 6: Handling in environmental laboratory (PROC 15)

### 9.1.7.1. Conditions of use

CS6 covers the analysis of liquid waste samples (see CS9 for the sampling procedure) containing EDC in the environmental control laboratory. Approximately 90 samples are collected during each production campaign. Concentration of EDC varies between 5% and 15%. Sampling occurs once per day during production, but samples are analysed weekly on a batch basis (7 samples per batch). Samples are received in 250ml glass bottles and stored in a designated vented cabinet in the environmental control laboratory pending analysis. EDC composition of the liquid waste sample is determined by GC analysis. Transfer of material from the sample bottle into the 2 ml GC vial for analysis is conducted within the fumehood. The sealed GC vials are then transferred to the GC auto sampler tray for analysis. When all tests are complete, surplus sample material, bottles, vials are transferred to a HDPE solvent waste drum for eventual incineration.

Sample preparation time for analysis of a weekly batch of samples is approximately one hour, and <1 hour is required for disposal and clean-up. The total time for the analysis could be 8-10 hrs with the GC run lasting approximately 8-9 hrs. However there is no exposure to the analyst during the GC run time.

| **Product characteristics** |
|---|
| • 1,2-dichloroethane – liquid (up to 15%) |
| **Amount used, frequency and duration of use/exposure** |
| • Weekly analysis during production campaign (3 months), 15 analyses per year, 2 hour exposure period per day of analysis |
| **Technical and organisational conditions and measures** |
| • Local exhaust ventilation: fume cupboard |
| **Conditions and measures related to personal protection, hygiene and health evaluation** |
| • Dermal Protection: yes (effectiveness: 95%) |
| • Respiratory Protection: none |
| **Other conditions affecting workers exposure** |
| • Place of use: Indoor – 10 ACH |

### 9.1.7.2. Exposure and risks for workers

CS6 covers the analysis of liquid waste samples containing EDC in the environmental control laboratory. Samples collected during the week are analysed in a single batchduring one day of the week. Total task duration involving GC analysis is up to 10 hours, but handling of EDC under the fumehood is restricted to a much shorter time period (assumed to be 2 hours). The remainder of the time is dedicated to GC runs. The laboratory analyst is not exposed to EDC for the remainder of the 12-hour shift. There is 1 laboratory analyst involved in the analysis of waste sample material (not involved in other CSs).

**Inhalation exposure assessment**

Exposure was modelled using the tier 2 ART.

ART input parameters (see Appendix 3):

- Activity 1 = laboratory – duration 80 mins (No exposure period = 400 mins) (80 min duration was chosen, as ART assumes 8 hour shifts; the calculated average concentration for 80 min/8 hours is equivalent to an exposure duration of 2 h during a 12 hours-shift)
  Activity model: transfer of falling liquids, flow <0.1 l/min which is adequate for transfers of small volumes in the laboratory (sample flask < 500 ml). Splash loading in an open process was chosen as worst case. Fume cupboards are used for all EDC handling. ACH 10 is assumed. Max. EDC concentration is 15%.

An exposure estimate of **0.082 mg/m$^3$** (upper limit of inter-quartile confidence interval to the 75th percentile; the 90$^{th}$ percentile amounts to 0.07 mg/m$^3$) is obtained with ART (see Appendix 3).

Two personal sampling long-term measurements were performed with two laboratory staff members from the quality control laboratory, handling neat EDC samples, in December 2014 and January 2015, resp. Both results were below the limit of quantification (LOQ=3 µg, i.e. <0.288 mg/m$^3$ and <0.183 mg/m$^3$, respectively). Even lower exposures can be expected in the environmental control laboratory scenario where EDC concentrations in samples do not exceed 15% compared to the quality control laboratory where EDC concentration ranges from 80% to 99.9%. These mesurements support the results from ART modelling.

**Dermal exposure assessment**

It is assumed that during one shift (2 hour) up to 16 splashes may occur, where liquid contents from samples drop on the gloves.
The procedure to estimate dermal exposure to EDC and to consider evaporation of the substance is described in Section 9.0.4.2.2 and Appendix 4.

**Table 32. Task-specific dermal exposure assessment**

| **Parameter** | **Unit** | **PROC 15** |
|---|---|---|
| Dermal dose per event (potential), product | µg/kg | 0.033 |
| Number of events per day | 1/d | 16 |
| Dermal dose per day (potential), product | µg/(kg x d) | 0.53 |
| Concentration of EDC in product | % | 15% |
| Dermal EDC exposure, (potential) | µg/(kg x d) | 0.08 |
| Efficiency of PPE (gloves) | % | 95% |
| **Dermal EDC exposure (actual)** | **µg/(kg x d)** | **0.004** |

* All values rounded to two significant figures, but unrounded values were taken for calculation.

**Exposure and risk estimate**

**Table 33. Exposure concentrations and risks for workers (CS6)**

| Route of exposure | TWA 12 h exposure concentration | Correction factor for frequency | corrected long-term exposure concentration | Excess cancer risk |
|---|---|---|---|---|
| Inhalation | 0.082 mg/$m^3$ | 0.09* | 0.0074 mg/$m^3$ | 4.4 x $10^{-6}$ |
| Dermal | 0.004 µg/(kg x d)** | 0.09* | 0.0004 µg/(kg x d) | 1.5 x $10^{-9}$ |
| Combined routes | | | | 4.4 x $10^{-6}$ |

** Frequency: activity takes place 15 times per year (166 days), correction factor = 0.09*

*** Gloves are used during exposure-related activities (95% efficiency)*

## 9.1.8. Worker contributing scenario 7: Storage tank EDC sampling (PROC 8b)

### 9.1.8.1. Conditions of use

CS7 covers routine sampling of EDC storage tanks. Regardless of whether a Raloxifene Hydrochloride production campaign is running, the storage tanks are sampled 4 times per year (see Figure 3, Appendix 6). 300ml clear glass bottles are used to collect the sample from the tank. PPE requirements for the task - disposable coveralls, neoprene gloves, full face respirator with an appropriate cartridge. Two samples are obtained, the first is a discard sample to ensure that the second sample presented to the QC laboratory for anlysis is free from moisture and extraneous matter. Contents of the discard sample are disposed of into the liquid waste solvent sink which is located inside a laboratory fumehood.

| **Product characteristics** |
|---|
| • 1,2-dichloroethane – liquid, neat |
| **Amount used, frequency and duration of use/exposure** |
| • 4 times per year, 15 minutes. |
| **Technical and organisational conditions and measures** |
| • Containment: sampling bottle screwed to filling line |
| • Local exhaust ventilation: none |
| **Conditions and measures related to personal protection, hygiene and health evaluation** |
| • Dermal Protection: yes, (effectiveness: 95%)<br>• Respiratory Protection: yes, (effectiveness: 95%) |
| **Other conditions affecting workers exposure** |
| • Place of use: outdoors |

### 9.1.8.2. Exposure and risks for workers

**Inhalation exposure assessment**

Exposure was modelled using the tier 2 ART.

ART input parameters (see Appendix 3):

Activity 1 = sampling of EDC – duration 15 mins; there is no EDC exposure during the remaining 465 min of the shift.

Justification of inputs used in ART model:
Emission source is located in the breathing zone of the worker. The activity class is transfer of falling liquid with a flow of 0.1 to 1 l/min which is relevant for bottle sampling (300 ml of EDC sampled). Splash loading in an open process has been chosen with medium containment, as a device is used where the flask is closely screwed to the line.

An exposure estimate of 0.021 mg/m$^3$ (result without PPE efficiency; upper limit of inter-quartile confidence interval to the 75$^{th}$ percentile; the 90$^{th}$ percentile amounts to 0.024 mg/m$^3$) is obtained with ART (see Appendix 3). The exposure result considering RPE efficiency 95% is **1.05 µg/m$^3$**.

**Dermal exposure assessment**

It is assumed that during one sampling activity 1 splash may occur, where liquid drops on the gloves (e.g. when unscrewing the bottle).

The procedure to estimate dermal exposure to EDC and to consider evaporation of the substance is described in Section 9.0.6.2.2 and Appendix 4.

**Table 34. Task-specific dermal exposure assessment**

| **Parameter** | **Unit** | **PROC 8b** |
|---|---|---|
| Dermal dose per event (potential), product | µg/kg | 1.3 |
| Number of events per day | 1/d | 1 |
| Dermal dose per day (potential), product | µg/(kg x d) | 1.3 |
| Concentration of EDC in product | % | 100 |
| Dermal EDC exposure, (potential) | µg/(kg x d) | 1.3 |
| Efficiency of PPE (gloves) | % | 95 |
| **Dermal EDC exposure (actual)** | **µg/(kg x d)** | **0.066** |

* All values rounded to two significant figures, but unrounded values were taken for calculation.

**Exposure and risk estimate**

**Table 35. Exposure concentrations and risks for workers (CS7)**

| Route of exposure | TWA 12 h exposure concentration | Correction factor for frequency | corrected long-term exposure concentration | Excess cancer risk |
|---|---|---|---|---|
| Inhalation | 1.05 µg/m$^3$ ** | 0.004* | 0.0042 µg/m$^3$ | 2.5 x 10$^{-9}$ |
| Dermal | 0.066 µg/(kg x d)** | 0.004* | 0.0003 µg/(kg x d) | 1.1 x 10$^{-9}$ |
| Combined routes | | | | 3.6 x 10$^{-9}$ |

** Frequency: activity takes place four times per year (166 d); correction factor = 0.024; as only one person out of the team of 6 tank farm operators is involved per event, the final correction factor is 0.024 x 1/6 = 0.004*

*** RPE and gloves used during exposure-related activities (95% efficiency)*

Due to the containment and low frequency of the activity, exposure levels are very low. Estimated risk from dermal exposure is close to that calculated for inhalation exposure.

## 9.1.9. Worker contributing scenario 8: Filter change out on Raw Solvent Storage Tank (PROC 8b).

### 9.1.9.1. Conditions of use

CS8 covers the specific operation of changing the filter on the raw solvent storage tank (see Figure 3, Appendix 6). Filters are changed every twelve months. The duration of the filter change task is 30 minutes. This task follows site practice for a filter change-out on solvent addition lines, which requires a nitrogen purge before opening the system under a line-break permit to ensure that solvent release is minimal. Filter change out instructions are outlined in a specific tank farm procedure. The discarded filter is placed in a sealed plastic liner in a fibre drum and sent off-site for incineration. During the task, the operator wears dermal and respiratory protection (see chapter 9.0.2.2).

| **Product characteristics** |
|---|
| • 1,2-dichloroethane – liquid, minute concentration |
| **Amount used, frequency and duration of use/exposure** |
| • Once per year, 30 minutes. |
| **Technical and organisational conditions and measures** |
| • Filter size: 1.5 $m^2$ |
| **Conditions and measures related to personal protection, hygiene and health evaluation** |
| • Dermal Protection: yes (effectiveness: 95%)<br>• Respiratory Protection: yes (effectiveness: 95%) |
| **Other conditions affecting workers exposure** |
| • Place of use: outdoors |

### 9.1.9.2. Exposure and risks for workers

**Inhalation exposure assessment**
Exposure was modelled using the tier 2 ART.

ART input parameters (see Appendix 3):

Duration: 20 mins (No exposure period = 460 mins) (20 min duration was chosen, as ART assumes 8 hour shifts; the calculated average concentration for 20 min/8 hours is equivalent to an exposure duration of 30 min/12 hours)
Justification of inputs used in ART: Concentration of EDC: 100%
Surface <1 -, according to sizes of filters changed (0.4 – 0.6 $m^2$)
Contamination of <10 % of surface (due to nitrogen purge)
No localised controls and no containment were assumed (operation carried out outside, close to buildings).

An exposure estimate of 9.5 mg/$m^3$ (result without PPE efficiency considered; upper limit of inter-quartile confidence interval to the 75$^{th}$ percentile; the 90$^{th}$ percentile amounts to 11 mg/$m^3$) is obtained with ART (see Appendix 3). The exposure result considering RPE efficiency 95% is **0.475 mg/$m^3$**.

**Dermal exposure assessment**

It is assumed that during the activity 10 splashes may occur, where liquid drops on the gloves.

The procedure to estimate dermal exposure to EDC and to consider evaporation of the substance is described in Section 9.0.6.2.2 and Appendix 4.

**Table 36. Task-specific dermal exposure assessment**

| **Parameter** | **Unit** | **PROC 8b** |
|---|---|---|
| Dermal dose per event (potential), product | µg/kg | 1.3 |
| Number of events per day | 1/d | 10 |
| Dermal dose per day (potential), product | µg/(kg x d) | 13.25 |
| Concentration of EDC in product | % | 100 |
| Dermal EDC exposure, (potential) | µg/(kg x d) | 13.25 |
| Efficiency of PPE (gloves) | % | 95 |
| **Dermal EDC exposure (actual)** | **µg/(kg x d)** | **0.66** |

* All values rounded to two significant figures, but unrounded values were taken for calculation.

**Exposure and risk estimate**

**Table 37. Exposure concentrations and risks for workers (CS8)**

| Route of exposure | TWA 12 h exposure concentration | Correction factor for frequency | corrected long-term exposure concentration | Excess cancer risk |
|---|---|---|---|---|
| Inhalation | 0.475 mg/$m^3$ ** | 0.001* | 0.475 µg/$m^3$ | 2.9 x $10^{-7}$ |
| Dermal | 0.66 µg/(kg x d)** | 0.001* | 0.00066 µg/(kg x d) | 2.8 x $10^{-9}$ |
| Combined routes | | | | 2.9 x $10^{-7}$ |

** Frequency: activity takes place once per year (166 d); correction factor = 0.006; as only one person out of the team of 6 EC&U operators is involved per event, the final correction factor is 0.006 x 1/6 = 0.001*

*** RPE and gloves used during exposure-related activities (95% efficiency)*

Due to the effective personal protection and the low frequency of the task (once per year) calculated risks are very low for this task.

## 9.1.10. Worker contributing scenario 9: Waste - Collection of a liquid waste sample from the incineration feed tanks (PROC 8b)

### 9.1.10.1. Conditions of use

CS9 covers the collection of a liquid waste sample from the incineration feed tanks. Samples are collected in 200 ml septum top glass bottles from an in-line needle type sampler, which is located within a glovebox (see Figure 10, Appendix 6). Peak EDC loading of the liquid waste storage system occurs during the Raloxifene Hydrochloride manufacturing campaign with typical EDC composition in the range 5-15%. When Raloxifene Hydrochloride Technical liquid waste stream has cleared the storage system typical EDC composition is neglible (<1%).

| |
|---|
| **Product characteristics** |
| • 1,2-dichloroethane – liquid, max. concentration 15% |
| **Amount used, frequency and duration of use/exposure** |
| • 90 times per year, 15 minutes. |
| **Technical and organisational conditions and measures** |
| • Containment: glovebox sampling |
| • Local exhaust ventilation: none |
| **Conditions and measures related to personal protection, hygiene and health evaluation** |
| • Dermal Protection: no<br>• Respiratory Protection: no |
| **Other conditions affecting workers exposure** |
| • Place of use: outdoors |

**9.1.10.2. Exposure and risks for workers**

**Inhalation exposure assessment**

Exposure was modelled using the tier 2 ART.
ART input parameters (see Appendix 3):

> Duration 15 mins (no exposure period = 465 min).
> Activity class: transfer of falling liquid with a flow of 0.1 to 1 l/min (adequate for bottle sampling, volume of samples: 300 ml). "Low specification glovebox" was chosen. EDC concentration: 15%.

An exposure estimate of 0.0011 mg/m$^3$ (upper limit of inter-quartile confidence interval to the 75$^{th}$ percentile; the 90$^{th}$ percentile amounts to 0.0012 mg/m$^3$) is obtained with ART (see Appendix 3).

**Dermal exposure assessment**

During sampling with the glovebox no EDC exposure is expected to occur. No dermal exposure assessment is performed.

**Exposure and risk estimate**

**Table 38. Exposure concentrations and risks for workers (CS9)**

| Route of exposure | TWA 12 h exposure concentration | Correction factor for frequency | corrected long-term exposure concentration | Excess cancer risk |
|---|---|---|---|---|
| Inhalation | 1.1 µg/m$^3$ | 0.09* | 0.099 µg/m$^3$ | 5.9 x 10$^{-8}$ |
| Dermal | - | - | - | - |
| Combined routes | | | | 5.9 x 10$^{-8}$ |

** Frequency: activity takes place 90 times per year (166 d); correction factor = 0.54; as only one person out of the team of 6 tank farm operators is involved per event, the final correction factor is 0.54 x 1/6 = 0.09*

Due to the containment (glovebox sampling), exposure levels are very low.

## 9.1.11. Worker contributing scenario 10: Waste - Changing filters on the incinerator feed line (PROC 8b).

### 9.1.11.1. Conditions of use

CS9 covers the changing of filters on the incinerator feed line. There is a filtration unit installed on the incinerator feed line to prevent the incinerator guns from blocking. EC&U operators are responsible for the cleaning and operation of this unit. Equipment setup is such that it is possible to flush and purge with nitrogen prior to breaking into the sytem under a line break permit. Change out of the filters takes place within a glovebag (see Figure 11, Appendix 6). This operation is performed once every two weeks. The duration is 30 minutes (maximum). During the task, the operator is wearing dermal and respiratory protection (see Section 9.0.2.2).

| **Product characteristics** |
|---|
| • 1,2-dichloroethane – liquid, conc.: extremely small (after flushing) |
| **Amount used, frequency and duration of use/exposure** |
| • Every two weeks, up to 30 min per event |
| **Technical and organisational conditions and measures** |
| • Containment: glovebag |
| • Local exhaust ventilation: none |
| **Conditions and measures related to personal protection, hygiene and health evaluation** |
| • Dermal Protection: no<br>• Respiratory Protection: yes (effectiveness: 90%) |
| **Other conditions affecting workers exposure** |
| • Place of use: outdoors |

### 9.1.11.2. Exposure and risks for workers

**Inhalation exposure assessment**

Exposure was modelled using the tier 2 ART.

ART input parameters (see Appendix 3):

- Duration 20 mins (no exposure period = 460 mins) (20 min duration was chosen, as ART assumes 8 hour shifts; the calculated average concentration for 20 min/8 hours is equivalent to an exposure duration of 30 min/12 hours)
  Before any dismantlement, the equipment is fully flushed and purged with nitrogen; therefore, the potential residual EDC is assumed to be extremely small (EDC conc. 0.1 - 0.5 %. Activity description: handling of contaminated objects with surface 1 - 3 $m^2$ (filter size is 1.6 $m^2$) with a contamination of 10 to 90 % of surface. Handling is performed within glovebag. Activity takes place outside.

An exposure estimate of 2.9 µg/$m^3$ (result without PPE efficiency considered; upper limit of inter-quartile confidence interval to the 75$^{th}$ percentile; the 90$^{th}$ percentile amounts to 3.3 µg/$m^3$) is obtained with ART (see Appendix 3). Considering personal RPE (90% efficiency) results in an exposure concentration of **0.29 µg/$m^3$**.

**Dermal exposure assessment**

During handling filters within the glovebag, no EDC exposure is expected to occur. No dermal exposure assessment is performed.

**Exposure and risk estimate**

**Table 39. Exposure concentrations and risks for workers (CS10)**

| Route of exposure | TWA 12 h exposure concentration | Correction factor for frequency | corrected long-term exposure concentration | Excess cancer risk |
|---|---|---|---|---|
| Inhalation | 0.29 µg/m$^3$ ** | 0.026* | 0.004 µg/m$^3$ | 2.4 x 10$^{-9}$ |
| Dermal | - | - | - | - |
| Combined routes | | | | 2.4 x 10$^{-9}$ |

** Frequency: activity takes place every two weeks (26 times per year); correction factor = 26/166=0.16; as only one person out of the team of 6 tank farm operators is involved per event, the final correction factor is = 0.027*

*** RPE used during exposure-related activities (90% efficiency)*

Due to the containment (glovebag), exposure levels are very low.

# 10. RISK CHARACTERISATION

## 10.1. Human health

### 10.1.1. Workers

As described in chapter 9, there is combined exposure for groups of worker engaged in more than one contributing scenario:

| **Job Title** | **CS Combinations:** |
|---|---|
| IE8 Operator | CS1 + CS3 + CS4 |
| EC&U Operator | CS2 + CS7 + CS8 + CS9 + CS10 |
| IE9 Maintenance Fitter | CS4 |
| Contract Maintenance Fitter | CS4 |
| In-process QCL analyst | CS5 |
| Environmental laboratory analyst | CS6 |

**Table 40. Calculation of combined risks for workers per contributing scenario**

| Contributing scenario | Exposed group | Associated excess cancer risk | Associated excess cancer risk (combined) |
|---|---|---|---|
| CS1 | IE8 operators (N=10) | $1.2 \times 10^{-5}$ | |
| CS3 | | $7.5 \times 10^{-6}$ | |
| CS4 | | $2.2 \times 10^{-6}$ | |
| Combined risks | | | $2.2 \times 10^{-5}$ |
| CS4 | IE9 Maintenance Fitters (N=6) | $2.2 \times 10^{-6}$ | $2.2 \times 10^{-6}$ |
| CS4 | Contract Maintenance Fitters (N=7) | $2.2 \times 10^{-6}$ | $2.2 \times 10^{-6}$ |
| CS2 | EC&U Operators (N=6) | $7.4 \times 10^{-6}$ | |
| CS7 | | $3.6 \times 10^{-9}$ | |
| CS8 | | $2.9 \times 10^{-7}$ | |
| CS9 | | $5.9 \times 10^{-8}$ | |
| CS10 | | $2.4 \times 10^{-9}$ | |
| Combined risks | | | $7.8 \times 10^{-6}$ |
| CS5 | In-process QCL analysts (N=6) | $4.8 \times 10^{-6}$ | $4.8 \times 10^{-6}$ |
| CS6 | Environmental Lab analyst (N=1) | $4.4 \times 10^{-6}$ | $4.4 \times 10^{-6}$ |

Low exposures were measured and/or modelled for all contributing scenarios. Exposure levels associated the main contributing scenario (CS1) for IE8 Operators during routine production of Raloxifene Hydrochloride Technical lead to a calculated risk close to $1 \times 10^{-5}$. Exposure levels and risks for other contributing scenarios are even lower. In conclusion, low exposures and risks are derived for handling EDC under these mostly closed conditions.

### 10.1.2. Exposure of humans via the environment

The following table summarise the results of the assessment of exposure of humans via the environment, as presented in Section 9.1.1.

**Table 41. Risk estimates for humans via the environment**

| Scale | Inhalation exposure | Oral exposure | Total exposure |
|---|---|---|---|
| Regional assessment | $7.42 \times 10^{-13}$ | $2.63 \times 10^{-13}$ | $1.00 \times 10^{-12}$ |
| Local assessment | $1.29 \times 10^{-09}$ | $3.00 \times 10^{-10}$ | $1.59 \times 10^{-09}$ |

The calculated risks in the regional assessment are extremely low and at least six orders of magnitude lower than the “indicative tolerable risk level” of $10^{-6}$ for the general population (ECHA, 2012a). In the local assessment, the risk from total exposure is almost three orders of magnitude lower than this “indicative tolerable risk level” and is dominated by the contribution of inhalation exposure (81% of total exposure).

## 10.2 Environment

Environmental risks are not considered.