Chemical Safety Report

Public Version

Legal name of applicant: MeiraGTX UK II Limited

Submitted by: MeiraGTX UK II Limited

Substance: 4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated [covering well-defined substances and UVCB substances, polymers and homologues]

Use title: Use of 4-tert-OPnEO as a manufacturing aid in the production of gene therapies

Use number: 1

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Declaration

The Applicant is aware of the fact that evidence might be requested by the Health and Safety Executive to support information provided in this document.

Also, we request that the information blanked out in the "public version" of the Chemical Safety Report is not disclosed. We hereby declare that, to the best of our knowledge as of today (15th January 2021) the information is not publicly available, and in accordance with the due measures of protection that we have implemented, a member of the public should not be able to obtain access to this information without our consent or that of the third party whose commercial interests are at stake.

Signature: 

Date, Place: 18TH JAN 2021
LONDON
UK

9. Exposure Assessment

9.1. Introduction

MeiraGTx UK II Ltd (the applicant) is a clinical-stage gene therapy company focused on developing potentially curative treatments for patients living with serious diseases.

The state-of-the-art manufacturing facility on Britannia Walk in Hoxton, London, UK, completed in early 2018, is designed to meet global regulatory requirements, including the current good manufacturing practices (cGMP) required by the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK and the US Food and Drug Administration (FDA). The facility holds a licence from the MHRA to manufacture investigational gene therapy products and gene therapy products for use on an off-label "Specials" basis. The 29,000-square foot facility has the flexibility and capacity to produce enough product for all the applicant's clinical trials and for the smaller markets, provide commercial material.

The applicant has developed gene therapies where 4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated (4-tert-OPnEO) is used as a manufacturing aid. 4-tert-OPnEO is on the authorisation list under the requirements of the REACH Regulation 1907/2006, and has a sunset date of 4th January 2021. Unless authorisation is granted by the relevant authorities, or an exemption applies, 4-tert-OPnEO cannot be sold or used in the United Kingdom after the sunset date.

4-tert-OPnEO was added to the REACH authorisation list due to concerns regarding its environmental impact. The environmental fate and behaviour and potential environmental effects of 4-tert-OPnEO were assessed by ECHA. (1) 4-tert-OPnEO is degraded to 4-tert-OP in wastewater, aquatic sediments and soils, a substance that is identified to be of very high concern due to potential endocrine disrupting properties and the potential or serious effects on the environment. As a concern has only been identified for the environment, a risk assessment for solely this aspect is presented in this CSR and a worker exposure assessment has not been performed as it is considered beyond the scope of this assessment and not relevant in the Annex XV dossier.

This environmental exposure assessment and risk characterisation has been performed in accordance with the relevant guidance for the production of a CSR under the REACH Regulation (2) considering specific aspects relating to the applicant's use.

9.1.1. Overview of uses

Tonnage Information

A maximum of a batches are manufactured per year at the applicant's site in London. For each batch a fresh a bottle of 4-tert-OPnEO is used. The assessed tonnage is therefore <0.1 (a) tonnes/year.

Table 9-1 provides the tonnage used in the assessment for each environmental contributing activity.

Table 9-1: Tonnage for assessment

ES#	Exposure scenario (ES) name and related environmental contributing scenarios	Tonnage per use (t/year)*	Daily local tonnage (t/day)*	Annual local tonnage (t/year)*
ES1	ES 1: Use of 4-tert-OPnEO in the development of gene therapies	a	a	a

*Based on a density of 1.07 g/cm^3

9.2. Introduction to the assessment for the environment

9.2.1. Scope and type of assessment for the environment

The environmental fate and behaviour and potential environmental effects of 4-tert-OPnEO were assessed by ECHA. (1) 4-tert-OPnEO is degraded to 4-tert-OP in wastewater, aquatic sediments and soils. This was identified as a substance of very high concern (SVHC) due to potential endocrine disrupting properties and the potential for serious effects on the environment. *In vitro* data on OPnEO and NPnEO and long-term fish toxicity data on NPnEO were summarised, and it was concluded that the substances possess oestrogenic activity in vitro and that they may induce in vivo endocrine activity. Thresholds for such endocrine effects were not established in the in vivo studies. Ecotoxicity data are summarised in the safety data sheet (SDS) for 4-tert-OPnEO, and predicted no-effect concentrations (PNECs) are presented in the Environmental Risk Evaluation Report for 4-tert-OP. (3) These data, however, are standard acute and chronic aquatic toxicity data; these, and the PNECs defined in the Environment Agency Report, do not address endocrine mediated effects. The available database therefore does not provide adequate information to set a PNEC for endocrine effects.

The approach taken in this CSR therefore follows a non-threshold qualitative approach and will aim to demonstrate that the applicant's use will result in negligible environmental exposure. The negligible impact will be demonstrated based on the low levels of 4-tert-OPnEO used at the manufacturing site in combination with appropriate risk management measures. Where possible the assessment uses specific information relevant to the applicant's site in London, UK.

Table 9-2: Type of risk characterisation required for the environment

Protection target	Risk characterisation type	
Fresh water	Qualitative, non-threshold	PEC_{local} value calculation
Sediment (freshwater)	Qualitative, non-threshold	PEC_{local} value calculation
Marine water	Qualitative, non-threshold	PEC_{local} value calculation
Sediment (marine water)	Qualitative, non-threshold	PEC_{local} value calculation
Sewage Treatment Plant	Qualitative, non-threshold	PEC_{local} value calculation
Air	Qualitative, non-threshold	PEC_{local} value calculation
Agricultural soil	Qualitative, non-threshold	PEC_{local} value calculation

9.2.2. Fate and distribution parameters

Physicochemical properties used for exposure estimation

The substance properties for 4-tert-OP are given in Table 9-3. These data were used in the European Union System for the Evaluation of Substances (EUSES 2.2.0) software for the fate estimation, and are taken from the Environmental Risk Evaluation Report for 4-tert-OP. (3)

Table 9-3: 4-tert-OP key physicochemical and fate properties

Substance property	**Value**
Molecular weight	206.33
Melting point	80.5 °C
Boiling point	281.5 °C
Vapour pressure	0.21 Pa at 20 °C
Partition coefficient (Log Kow)	4.12 at 20.5 °C
Density	1.07 g/cm^3
Water solubility	19 mg/L at 22 °C (EUSES allows solubility at 20 or 25°C – entered at 20°C as a worst case)
Henry's law constant (in Pa m^3/mol)	3.003 at 25°C Calculated in EUSES 2.2
Biodegradation in water: screening tests	Not readily biodegradable
Bioaccumulation: BCF (aquatic species)	633.9 L/kg wwt Calculated in EUSES 2.2
Adsorption/Desorption: Koc at 20 °C	2740 ml/g Calculated in EUSES 2.2 using the OSAR predominantly hydrophobic

In accordance with the decision made during a meeting of ECHA's Committee for Risk Assessment (RAC) in December 2017 (4), a worst-case approach has been taken which assumes that all 4-tert-OPnEO is converted to 4-tert-OP in the environment.

The quantity of 4-tert-OPnEO released to the environment was adjusted in order to express environmental concentrations as 4-tert-OP. Based on the difference in molecular weights (206.33(4-tert-OP)/625 (4-tert-OPnEO[9.5 ethoxylate units]), the correction factor used is 0.33.

Fate (release percentage) in the modelled biological sewage treatment plant

In a standard (modelled) biological sewage treatment plant (STP), the emissions are distributed in the following way:

Release to water	71.51%
Release to air	2.896%
Release to sludge	25.594%
Release degraded	0%

The above fractions are calculated by the SIMPLETREAT 4 model integrated in EUSES 2.2.0.

9.3. Exposure scenario 1, Environment

Use as a manufacturing aid in the production of gene therapies

Environment contributing scenario(s):	
ES 1: Use of non-reactive processing aid at industrial site (no inclusion into or onto article)	ERC 4
Worker contributing scenario(s):	Not relevant

Further description of the use

4-tert-OPnEO is used as a manufacturing aid in the production of gene therapies. A simple process flow is illustrated in Figure 9-4. Further specific details on the process are also given in Figure 9-5 to Figure 9-8.

The use of 4-tert-OPnEO takes place in an underground facility and is therefore used in an isolated environment, with the substance only being transferred by trained personnel between controlled storage and the manufacturing cleanrooms. The facility is built to industry best practices for sustainability. Employees are trained in all relevant standard operating procedures (SOPs) and operate to cGMP which ensures rigorous control of manufacturing operations and documentation. This includes storage, handling, cleaning, facility material flows, plus the production and disposal of hazardous and biohazardous substances. Operator training and certification is documented and maintained in an electronic training management system. Procedures are in place to respond to any potential spillage of 4-tert-OPnEO that may occur.

Receipt and storage of 4-tert-OPnEO

4-tert-OPnEO is ordered from the supplier in 1 L glass bottles which are delivered to the applicant's warehouse in Wembley, London where they are stored. When required, the requisite number of bottles are transferred to the Britannia Walk manufacturing site by an external contractor.

When received at the manufacturing site the bottles are transferred from the delivery vehicle via trolley or via hand to the store within the warehouse above ground, where they are stored in a chemical cabinet.

When required for production a bottle is requested, the outer packaging is removed, and the bottle is cleaned per the SOP. The bottle is placed into a goods lift and sent down to the production facility on the lower floor, below ground. Transfer of the material follows the SOP for material flow. There will be no release of 4-tert-OPnEO to the environment from this process.

Figure 9-1: Bottle of 4-tert-OPnEO and cabinet in which bottles are stored at the Britannia Walk site

Processing Room

The lower level of the manufacturing site is sealed and environmentally controlled. For ventilation the viral rooms are recirculating air b fresh air. Corridors and other laboratories are ventilated once through and air discharged to atmosphere untreated. Most rooms have their own HVAC system monitored via a building management computer. The production process is defined in an SOP.

The bottles of 4-tert-OPnEO are transferred via an air lock into the Processing Room. b .

The excess b 4-tert-OPnEO in the bottle is transferred out of the room via the materials transfer hatch and transferred to the waste room (also below ground). It is treated as chemical waste and disposed of off-site by a contractor for hazardous waste incineration.

b

All apparatus b is then double-bagged and moved out of the room via the materials transfer hatches and transferred to the waste room.

All waste from this process is sent to hazardous waste incineration and the b . There will therefore be no release of 4-tert-OPnEO to the environment from this step of the process.

Cell Feeder Room / Bulk Virus Room

b

[redacted], approximately [redacted] containing ca [redacted] w/v 4-tertOPnEO) is rejected; is treated as chemical waste and disposed of off-site by a contractor for hazardous waste incineration (Figure 9-5).

[redacted] are assumed to be lost to wastewater.

The [redacted] from the [redacted], Figure 9-8). The final product from this process is the drug substance for formulation (containing [redacted] 4-tert-OPnEO). The other product is [redacted] of filter permeate which is assumed to be lost to wastewater. 4-tert-OPnEO is not detected in any samples above [redacted] w/v after the [redacted].

A maximum of [redacted] of 4-tert-OPnEO in total will be contained in those components lost to wastewater.

During this process numerous monitoring samples are taken from [redacted]. Samples taken throughout the process are sent to Quality Control for analysis following a set testing plan and are then sent to the waste room before being removed by a contractor for disposal off-site via hazardous waste incineration. Some samples are shipped to external contractors for testing; once testing is complete samples are disposed of as clinical waste via incineration.

All product contacting apparatus and material are single-use, these components are double-bagged and removed via the materials transfer hatches and transferred to the waste room. This is then removed by a contractor for disposal off-site by hazardous waste incineration.

The sole potential environmental release from the process arises from the [redacted]. For the purpose of the assessment a worst-case assumption has been made that these materials are lost to wastewater and contain a total of [redacted] of 4-tert-OPnEO per batch. This is via the single sink at the facility connected to the municipal sewerage system; all other waste is removed by a contractor for disposal off-site by hazardous waste incineration. 24 hours prior to release of any liquid waste to the sewerage system, it is treated with the disinfectant Virkon S to denature any biological material.

Final product

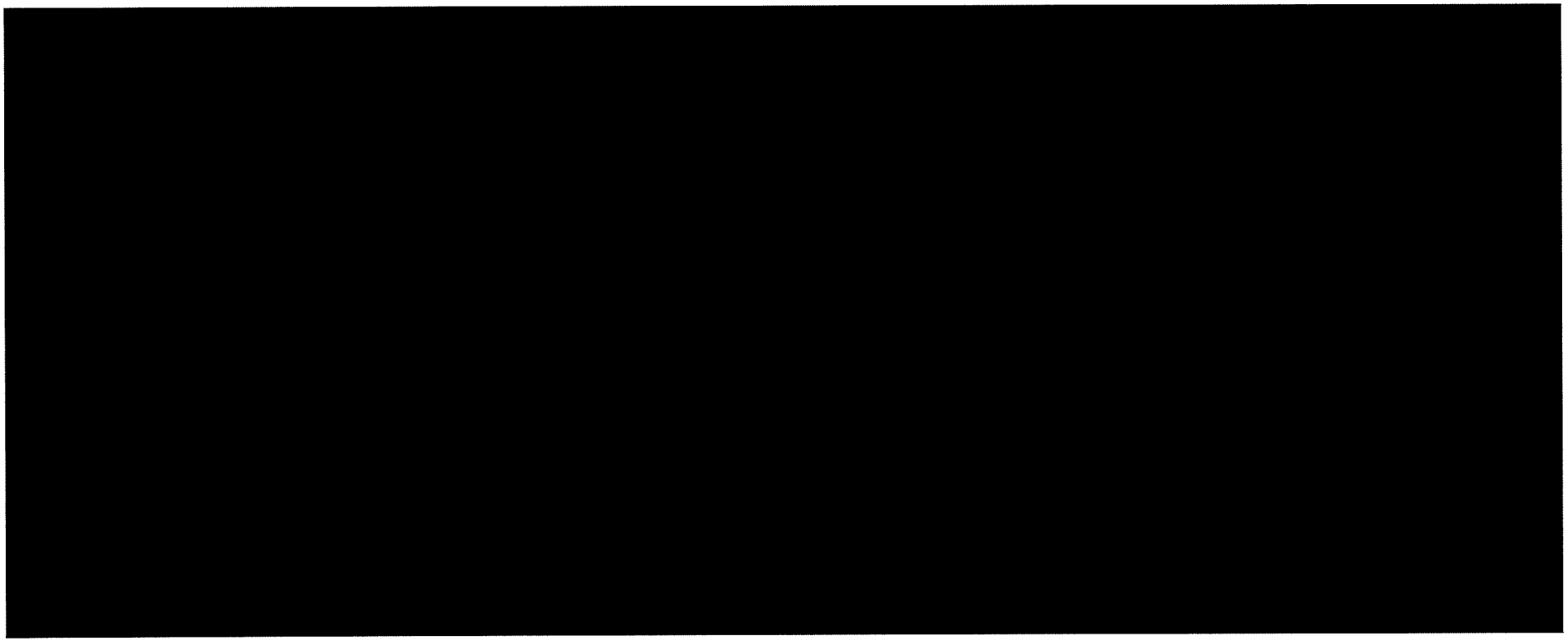
The final product is transferred from the room via the materials transfer hatch and sent to Quality Control for testing.

All samples taken for analysis are stored in accordance with SOP, and after analysis are sent to the waste room. Samples are then removed by a contractor for disposal off-site by hazardous waste incineration.

Figure 9-2: Hazardous waste ready for disposal by contractor

Figure 9-3: Drain connected to the municipal sewerage system that liquid waste is pumped into

Figure 9-4: b [redacted]



b [redacted]

Figure 9-5: b [redacted]

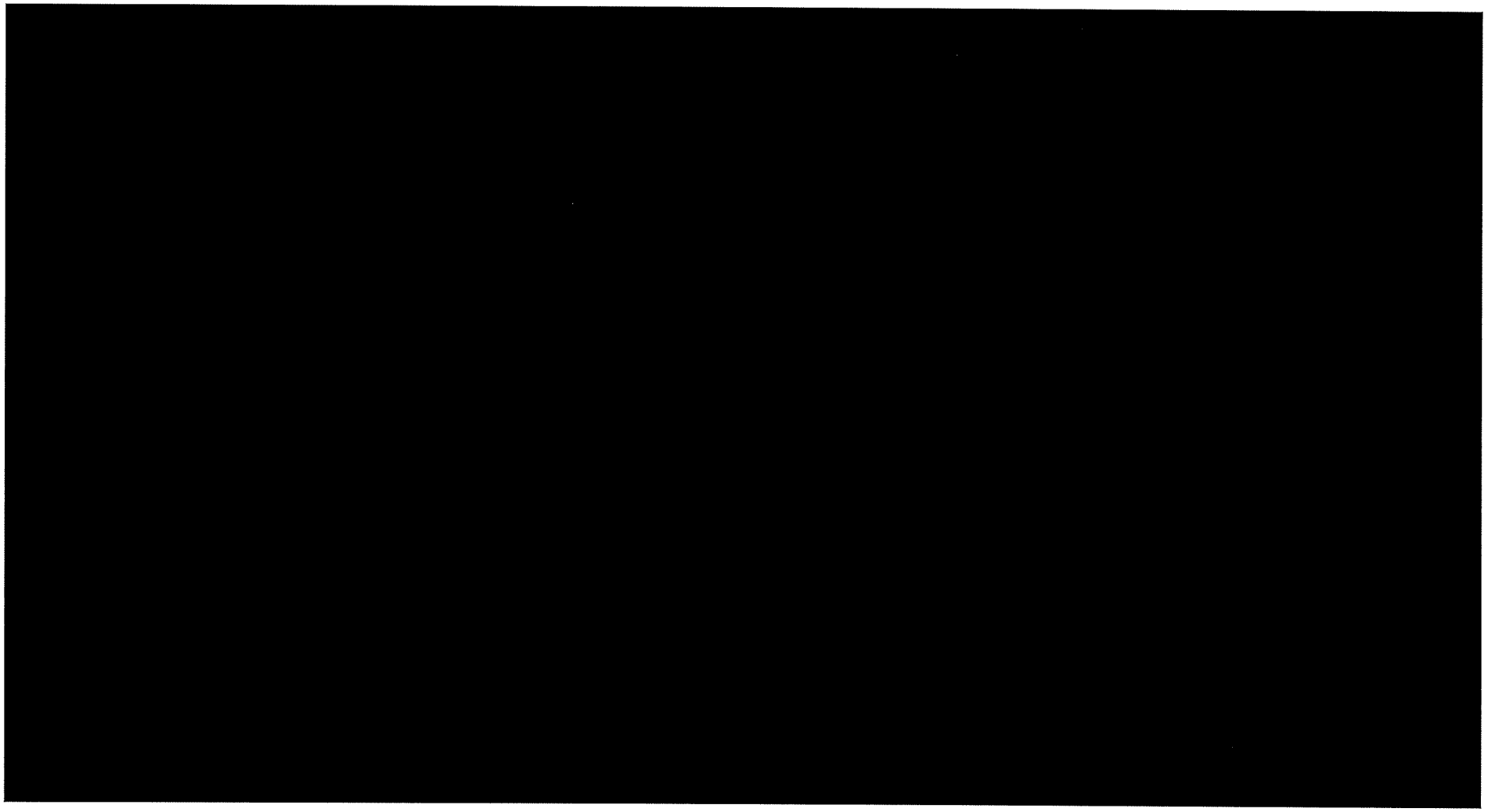


Figure 9-6: b [redacted]

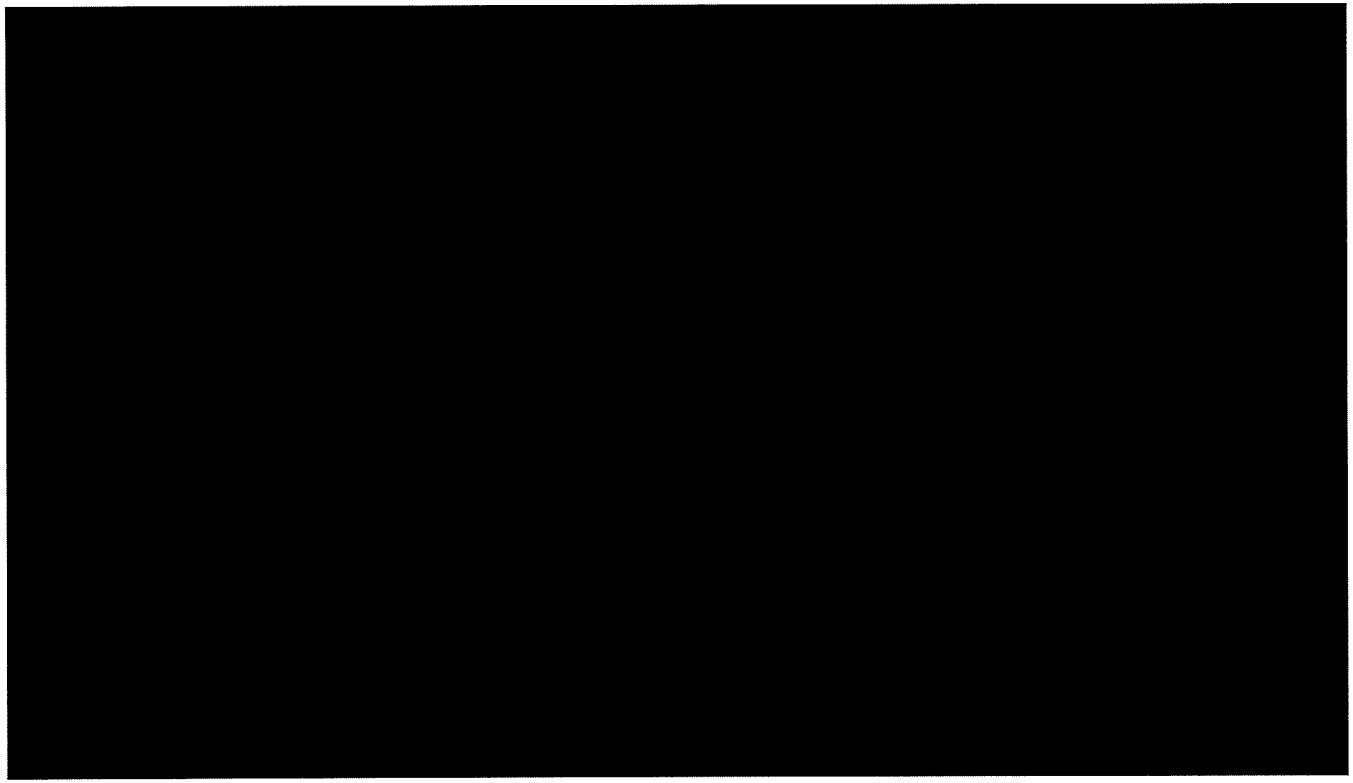


Figure 9-7: b [redacted]

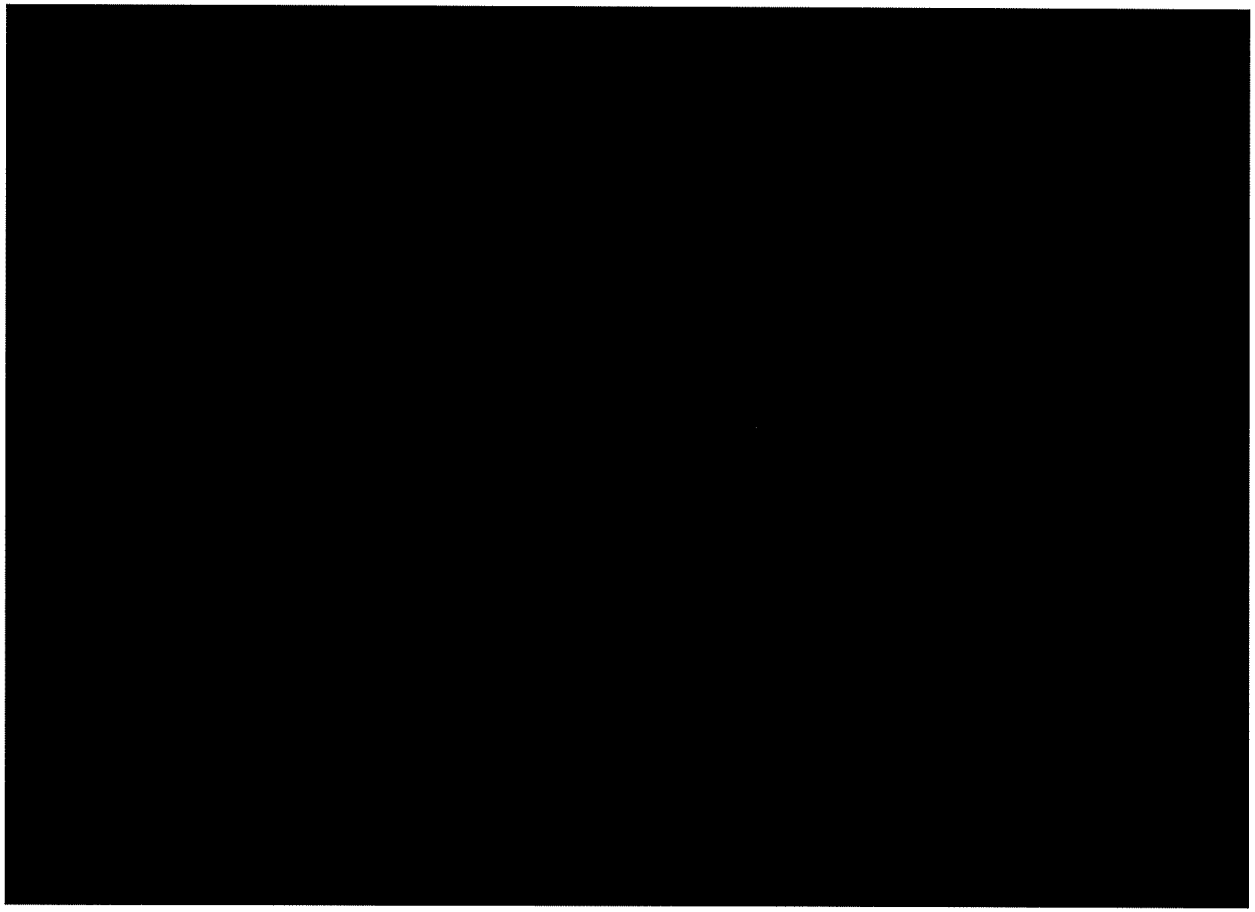
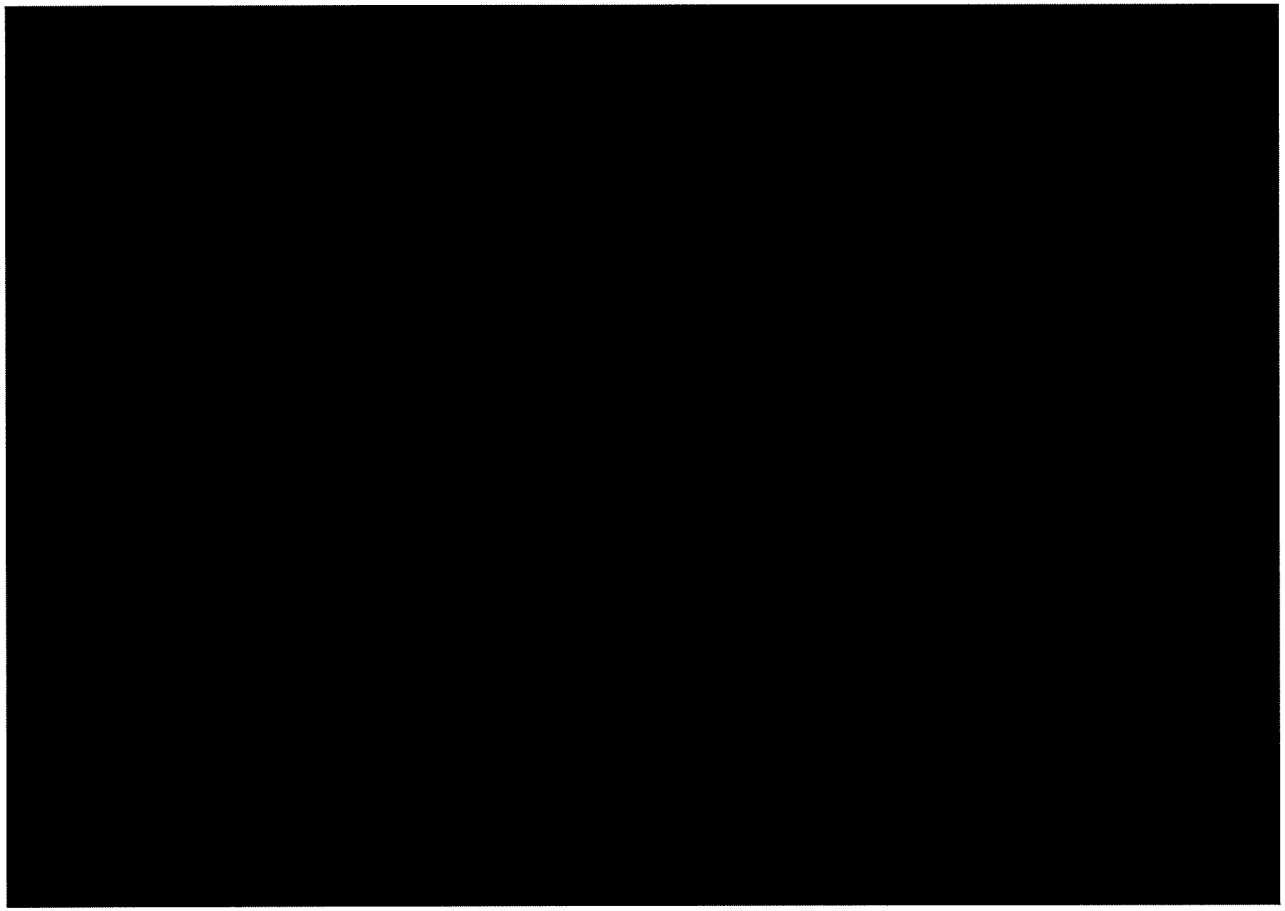


Figure 9-8: b [redacted]



Approach followed for the exposure scenario

a litres of 4-tert-OPnEO will be used at the manufacturing site in any one year. b of each bottle (b) is used in the manufacture of each batch and the remaining b is transferred to a contractor for hazardous waste incineration. Due to the controls in place for this hazardous waste incineration, it is assumed that the environmental release from this waste will be nil.

The majority of the 4-tert-OPnEO is lost in the b will be treated as chemical waste and disposed of off-site by a contractor for hazardous waste incineration. The sole potential environmental release from the process arises from the b which are lost to wastewater and contain a total of c 4-tert-OPnEO per batch.

A b,c release to wastewater is therefore assumed. Due to the nature of the use, the low volatility and the risk mitigation measures in place, releases to soil and air will be zero.

9.3.1. Environmental Contributing Scenario 1

Conditions of use

Amount used, frequency and duration of use (or from service life)
• Daily use amount at site: a,b,c *There will be a maximum of a batches run per year. Each batch will use a b bottle of 4-tert-OPnEO (total of a). It is assumed that, at most, the waste from b batches would be released to waste water on any single day, to give b emission days per year with a daily use of a,b,c tonnes.*
• Annual use amount at site: b,c tonnes/year *Based on a batches run per year each using a of 4-tert-OPnEO.*
Conditions and measures related to biological sewage treatment plant
• Biological STP: Standard [Effectiveness Water: 28.49%]
• Discharge rate of STP: >= 1209600 m^3/day *Wastewater from the manufacturing site is sent to the Beckton Sewage Treatment Plant. The average hydraulic flow of the Beckton sewage treatment plant is 14000 L/sec, equivalent to 1209600 m^3/day.* (5)
• Application of the STP sludge on agricultural soil: Yes
Conditions and measures related to external treatment of waste (including article waste)
• Particular considerations on the waste treatment operations: No (other reason) *Waste disposal according to national/local legislation is sufficient.*
Other conditions affecting environmental exposure
The unused 4-tert-OPnEO is collected by a waste contractor and is disposed of via hazardous waste incineration.
Other conditions affecting environmental exposure
• Receiving surface water flow rate: N/A *Default value – discharge will be from the Beckton Sewage Treatment Plant into the tidal part of the River Thames. Data on flow rate are not available, therefore a default 10X dilution was assumed.*

Releases

The local releases to the environment are reported in Table 9-4. Note that the releases reported do not account for the removal in the modelled biological STP.

Table 9-4: Local releases to the environment

Release	Release estimation method	Explanations
Water	Site specific	Release factor after on-site RMM: c % Local release rate: c kg 4-tert-OP/day Explanation: A b,c bottle of 4-tert-OPnEO is opened per batch. Only b,c of 4-tert-OPnEO is used in the process and it is assumed that c of this is released to wastewater per batch and the waste from a maximum of b batches would be released to wastewater in a single day. A conversion factor of 0.33 is then applied to account for the 100% conversion of 4-tert-OPnEO to 4-tert-OP. This conversion is based on the relative molecular weights of the two compounds. The unused 4-tert-OPnEO, b and the apparatus used is removed off-site by an external contractor for hazardous waste incineration. Complete destruction of the substance will occur via this process and there will be no release to wastewater.
Air	ERC	Release factor after on-site RMM: 0% Local release rate: 0 kg/day Explanation: There are no releases to air during the batch preparation process as the substance is non-volatile and the process takes place indoors in controlled areas. The unused 4-tert-OPnEO, b and the apparatus used is removed off-site by an external contractor for hazardous waste incineration. Complete destruction of the substance will occur via this process and there will be no release to wastewater.
Non-agricultural soil	ERC	Release factor after on-site RMM: 0% Explanation: There is no direct release to soil during the batch preparation process as it takes place indoors in controlled areas. The unused 4-tert-OPnEO, b and the apparatus used is removed off-site by an external contractor for hazardous waste incineration. Complete destruction of the substance will occur via this process and there will be no release to wastewater.

Releases to waste

Release factor to external waste:

It is assumed that c of 4-tert-OPnEO is discharged to wastewater during the preparation of each batch of the lysis buffer equating to b,c of the total amount used. A conversion factor of 0.33 is applied to this to express the release as 4-tert-OP.

The remaining unused [redacted] of the 4-tert-OPnEO ([redacted]), [redacted] will be collected by a contractor and sent off-site to hazardous waste incineration. Complete destruction of the substance will occur via this process and there will be no release to the environment.

Exposure and risks for the environment and man via the environment

The exposure concentrations are reported in Table 9-5. The exposure estimates have been obtained with EUSES 2.2.0 unless stated otherwise.

Table 9-5: Exposure concentrations and risks for the environment

Protection target	Exposure concentration – 4-tert-OP
Fresh water	Local PEC: 3.89 x 10-8 mg/L
Sediment (freshwater)	Local PEC: 2.34 x 10-6 mg/kg ww
Marine water	Local PEC: 5.43 x 10-9 mg/L
Sediment (marine water)	Local PEC: 3.27 x 10-7 mg/kg ww
Sewage Treatment Plant	Local PEC: 3.88 x 10-7 mg/L
Air	Local PEC: 4.72 x 10-10 mg m^3
Agricultural soil	Local PEC: 4.53 x 10-6 mg/kg ww

Risk characterisation

Predicted environmental concentrations for 4-tert-OP calculated using EUSES 2.2.0 are presented in Table 9-5 above. For the purposes of the calculation, worst case assumptions were used to ensure a precautionary assessment. These include the assumption that [redacted] of the 4-tert-OPnEO used in the formulation of the lysis buffer is released to wastewater from each batch and 100% of this is converted to 4-tert-OP. This will not be the case and concentrations will be lower than indicated above.

Technical controls are in place at the applicant's manufacturing site which will minimise environmental exposure. There is only one sink in the facility, and this is the sole source of environmental exposure via wastewater. The process takes place in a controlled environment in which releases to the outdoors are prevented. All unused 4-tert-OPnEO, [redacted] and apparatus used in the manufacturing process are disposed of to an external contractor for hazardous waste incineration off-site. [redacted] contains >[redacted] of the used 4-tert-OPnEO and detected levels are insignificant in subsequent steps; thus, only [redacted] of 4-tert-OPnEO may be released to wastewater per batch.

The state-of-the-art manufacturing facility, completed in early 2018, is designed to meet global regulatory requirements, including the current good manufacturing practices (cGMP) required by the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK and the U.S. Food and Drug Administration (FDA). The use of 4-tert-OPnEO takes place in an underground basement facility and is therefore used in an isolated environment, with the substance only being transferred (by trained personnel) between storage and the production room. The facility is built to industry best practices for sustainability.

Material quantities, status and locations are controlled using a Quality System, and employees are trained in company procedures on cGMP and standard operating procedures (SOPs). This includes storage, handling, cleaning, facility flow, production and disposal of hazardous and biohazardous substances. Operator training and certification is documented and maintained in an electronic

training management system. Procedures are in place to respond to any potential spillage of 4-tert-OPnEO that may occur.

Considering the risk management measures described above, a single waste stream is identified to wastewater that may result in an environmental release containing 4-tert-OPnEO. The applicant is currently investigating further measures to divert this release from the municipal sewerage system to ensure that emissions of 4-tert-OPnEO to the environment are as low as is technically and practically possible.

This assessment was conducted to demonstrate that the potential environmental concentrations of 4-tert-OP resulting from the applicant's use in the processes defined above are low. Commercial production has yet to begin, and so the assessment has been conducted using several estimates and assumptions. The assumptions used, however, are worst-case in order to take a conservative approach. It is expected that the emissions from the actual production process will be lower and measures are also being investigated to reduce any potential environmental release. The applicant is committed to conducting its operations and managing its products in a manner that is protective of the environment and minimises any impact on the environment and the workplace.

10. Risk Characterisation Related to Combined Exposure

10.1. Human health (related to combined exposure)

10.1.1. Workers

Not relevant, an assessment of the risk to workers has not been performed as it is considered beyond the scope of this assessment and not relevant in the Annex XV dossier.

10.1.2. Consumers

Not relevant, an assessment of the risk to consumers has not been performed as it is considered beyond the scope of this assessment and not relevant in the Annex XV dossier.

10.2. Environment (combined for all emission sources)

10.2.1. All uses (regional scale)

A combined exposure assessment is not necessary as this CSR is a site-specific assessment assessing solely a single exposure route arising from a single use.

10.2.2. Local exposure due to all wide dispersive uses

Not relevant – this CSR is a site-specific assessment assessing solely a single exposure route arising from a single use.

10.2.3. Local exposure due to combined uses at a site

Not relevant – this CSR is a site-specific assessment assessing solely a single exposure route arising from a single use.

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Appendix 1: Uncertainty Analysis

Uncertainty	Impact	Assumption
The actual release from the site is not known	The percentage release has a direct impact on the assessment	A precautionary approach has been taken in the assessment and a conservative release factor has been assumed in the assessment. This assumes that all 4-tert-OPnEO not sent to hazardous waste incineration is lost to wastewater. This ensures that the assessment is conservative. In reality releases will be lower than have been assumed in the assessment
The process is not yet commercialised. Therefore, variations in manufacturing practice after commercialisation could impact the usage of 4-tert-OPnEO and subsequent release	Changes manufacturing practice could have an impact on the potential environmental releases	The assessment is based on current practices as of 2020 and makes a number of worst-case assumptions. Manufacturing requires strict adherence to SOPs and thus it is unlikely that there will be significant variation in usage amounts.
The process is not yet commercialised and thus commercial production quantities are not known. This could lead to variation in the quantities 4-tert-OPnEO used and any subsequent release.	Changes in use quantities could have an impact on the potential environmental releases	The amount of 4-tert-OPnEO used is based on the maximum number of batches per year which can be produced by the manufacturing plant. As the maximum capacity has been assumed the assessment can be considered conservative.
The dilution factor in the River Thames at the Beckton STP outflow is not known	The water volume of the Thames affects the dilution at the STP outflow and subsequent PECs in surface water and sediment.	The default factor assuming 10X dilution was assumed in the assessment in the absence of site-specific data. Although the volume of the outflow at Beckton is large, the Thames at this point is of significant size (ca 550 m wide), tidal, with significant water volume and flow. An assumption of 10X dilution is therefore considered conservative.