CHEMICAL SAFETY REPORT

PUBLIC VERSION

Legal name of Applicant(s):	Abbott Laboratories Limited
Submitted by:	*Abbott Laboratories Limited*
Substance:	*4-(1,1,3,3-tetramethylbutyl) phenol, ethoxylated*
Use title:	*Professional use as a surfactant in the final use of In-Vitro Diagnostic Devices (IVDs) for clinical testing using ARCHITECT, Alinity and ABBOTT PRISM automated analyser systems.*
Use number:	*1*

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List of Abbreviations

4-tert-OPnEO	4-(1,1,3,3-tetramethylbutyl) phenol, ethoxylated
4-tert-OP	4-tert-octylphenol
BCF	Bioconcentration Factor
CAS	Chemical Abstract Service
CC	Clinical chemistry
CHESAR	Chemical Safety Assessment and Reporting tool
CLP	Classification, Labelling and Packaging
CSA	Chemical Safety Assessment
CSR	Chemical Safety Report
DW	Dry Weight
DU	Downstream Users
EC	European Community
ECHA	European Chemicals Agency
EEA	European Economic Area
ERC	Environmental Release Category
ES	Exposure Scenarios
EUSES	European Union System for the Evaluation of Substances
EWC	European Waste Catalogue
GB	Great Britain, made up of England, Scotland, and Wales
GHS	Globally Harmonised System
HIV	Human Immunodeficiency Virus
IA	Immunoassays
IUPAC	International Union of Pure and Applied Chemistry
IVD	In Vitro Diagnostic Device
ISO	International Organisation for Standardization
LAD	Latest Application Date
LOEC	Lowest Observed Effect Concentration
NOEC	No Observed Effect Concentration
OECD	Organisation for Economic Co-operation and Development
PC	Product Category
PNEC	Predicted No-Effect Concentration
PEC	Predicted Exposure Concentration
RAC	Committee for Risk Assessment
R&D	Research and Development
REACH	Registration, Evaluation, Authorisation and Restrictions of Chemicals
RMM	Risk Management Measures
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SEA	Socio-Economic Analysis
SD	Sunset Date
SIDS	Screening Information Dataset
SU	Sector of Use
STP	Sewage Treatment Plant
SVHC	Substances of Very High Concern
UK Reach	The REACH etc. (Amendment etc.) (EU Exit) Regulations 2019; SI 2019 No. 758
WDU	Wide Dispersive Use

Declaration

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

Also, we, Abbott Laboratories Limited, request that the information blanked out in the "public version" of the Chemical Safety Report is not disclosed. We hereby declare that, to the best of our knowledge as of today, **30th September 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:

Colleen O'Donnell — 30 Sep 21, Sligo Ireland

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9. EXPOSURE ASSESSMENT (and related risk characterisation)

Abbott is a worldwide healthcare company. Abbott has a broad range of branded generic pharmaceuticals, medical devices, diagnostics, and nutrition products. The Company's *in-vitro* diagnostics (IVD) business provides immunoassays, including blood screening products and clinical chemistry tests. Its medical tests and diagnostic instrument systems are used worldwide by hospitals, laboratories and blood banks for clinical diagnosis and monitoring diseases. Abbott manufactures a broad range of tests, including SARS-CoV-2, HIV, hepatitis, thyroid function, fertility and pregnancy, cardiology, renal and metabolic markers, therapeutic drug monitoring, detection of drugs of abuse, clinical chemistry assays and other indicators of health.

Abbott operates three manufacturing sites located within the EU, where the sites act as Downstream Users of the substances within the Annex XIV entry number 42, 4-(1,1,3,3-tetramethylbutyl) phenol, ethoxylated (4-tert-OPnEO) in the formulation of In-vitro Diagnostic Devices (IVDs). It also operates a dedicated distribution center (Abbott Diagnostics GmbH) from where IVD reagents are distributed to customers within and outside the EU. Abbott has applied for Authorisation under EU REACH (0167-02) for the manufacturing in, and distribution from, its EU entities as well as on behalf of its EU customers, which are also considered Downstream Users of 4-tert-OPnEO contained within the IVDs.

As a result of the United Kingdom (UK) withdrawal from the European Union (EU) in 2021, (Abbott Laboratories Limited, hereinafter known as 'the Applicant') is now applying for a bridging Authorisation for their Great Britain based customers under UK REACH. In the context of this assessment the Applicant includes customers based in Scotland, Wales and England (herein referred to as Great Britain or GB). As a result of the Northern Ireland (NI) Protocol, NI customers are not included as part of this application.

9.0 Introduction

9.0.1 Overview of uses and Exposure Scenarios

The Applicant has applied for one use of 4-tert-OPnEO.

- USE 1. Professional use as a surfactant in the final use of *In-Vitro* Diagnostic Devices (IVDs) for clinical testing using ARCHITECT, Alinity and ABBOTT PRISM automated analyser systems.

Use 1 occurs at over 130 hospital, clinical laboratory and blood banking sites distributed across GB. This use takes place in dedicated instruments for clinical testing of human samples.

4-tert-OPnEO is used in the final formulation of reagent, calibrator and control IVD kits. Reagent, Calibrator and Control IVD kits are referred to collectively as 'Reagents' throughout the CSR.

Tonnage information:

Assessed tonnage: 100 – 1000 ([redacted]) kg per year

The tonnage of OPnEO used by the Applicant's GB customers is calculated from the use quantity for the entire EEA (which included the UK). The UK use quantity was initially calculated from the EEA downstream professional use quantity identified in the Applicant's EU REACH application 0167-02, which included customers in the UK. The use quantity was extracted based on the number of the Applicant's tests distributed in the UK relative to that for the entire EEA. Number of tests is relevant as the EEA use quantity in the Applicant's EU REACH application was based on the average amount of 4-tert-OPnEO per test. The calculation used is as follows:

Former EEA Use 2 tonnage X (UK #tests / Former EEA #tests) = [redacted] kg X ([redacted]) = 10-100 ([redacted]) kg

The GB use quantity was estimated from the UK use quantity calculated above. The conversion from UK to GB use quantity was made using an adjustment for the percentage of the Applicant's analysers (excluding ABBOTT PRISM quantities) that are used in GB vs total UK ([redacted] percent) which are not included in this assessment.

GB use quantity = UK use quantity x (GB instrument placements / UK instrument placements) = [redacted] kg X ([redacted]) = 10-100 ([redacted]) kg

The GB value has been used for the exposure assessment in this document.

An additional 10 -100 ([redacted]) kg is used in GB ABBOTT PRISM reagents, bringing the total ES1 quantity to 100 -1,000 ([redacted]) kg (GB). Only one customer in GB is using the Applicant's ABBOTT PRISM analyser. The total amount of 4-tert-OPnEO was calculated using the number of kits forecast to be used by this customer through 2022, along with the amount of 4-tert-OPnEO contained within each product kit. No ABBOTT PRISM instruments are in use in Northern Ireland; therefore, this value is considered final for GB.

Table 9.0.1: Overview of exposure scenario and contributing scenario

Identifier*)	Market Sector	Titles of exposure scenarios and the related contributing scenarios	Use Quantity (kg /year OPnEO)
ES1-PW	-	Professional use as a surfactant in the final use of *In-Vitro* Diagnostic Devices (IVDs) for clinical testing using ARCHITECT, Alinity and ABBOTT PRISM automated analyser systems.	100 - 1000 ([redacted])
Professional end use: PW-#			

9.0.2 Introduction to the assessment

9.0.2.1 Environment

Scope and type of assessment:

The substance was originally added onto Annex XIV of EU REACH (Authorisation list) because it breaks down to 4-tert-Octylphenol that has endocrine disrupting properties for the environment. Annex XIV of EU REACH was retained in UK REACH (The REACH etc. (Amendment etc.) (EU Exit) Regulations 2019; SI 2019 No. 758) with the same Latest Application Date (LAD) and Sunset Date (SD). In this instance the Applicant is able to benefit from transitional provisions introduced in The REACH etc. (Amendment etc.) (EU Exit) (No. 3) Regulations 2019; SI 2019 No. 1144, allowing for adjustment of the LAD and SD to 1st July 2022.

A threshold (PNEC) for 4-tert-OPnEO is currently not available and as such a non-threshold qualitative approach is being taken in this assessment as indicated in Table 9.0.2 below. Evaluation of any potential health hazards to humans is not required within the framework of this authorisation application. Additionally, the Annex XV dossier for 4-tert-OPnEO and for 4-tert-OP (BAuA, 2012) details that there is no relevant information available regarding the potential endocrine effects for terrestrial organisms, in particular soil dwelling organisms or birds, and the authors concluded that they do not represent substances with strong endocrine disruption potency properties for the mammalian system.

A worst-case approach is employed in the environmental exposure assessment assuming that all quantities of 4-tert-OPnEO released to the environment are ultimately converted to 4-tert-OP. The environmental concentrations arising from the uses of 4-tert-OPnEO will be calculated based on the releases and the appropriate environmental fate parameters of the substance.

The professional use of the IVD kits (containing 4-tert-OPnEO) is carried out using ARCHITECT, Alinity, and ABBOTT PRISM instruments. Professional use occurs at over 130 customer (hospital, clinical laboratory and blood banking) sites distributed across GB.

Due to the high volumes of liquid waste generated, Architect and Alinity high throughput, fully automated analyser systems are typically plumbed directly to drain. All waste from the ABBOTT PRISM system is disposed of by incineration as confirmed with the GB customer. The following assumptions were used for the exposure assessments:

- Architect and Alinity instrument liquid waste was assumed to be disposed directly to drain.
- Residual solution from excess and expired material/partially empty Architect and Alinity containers was assumed to be disposed directly to drain.
- ABBOTT PRISM instrument solid biohazardous waste and residual solution from excess and expired/partially empty PRISM containers are disposed of by incineration.

Table 9.0.2: Type of risk characterisation required for the environment

Protection target	Type of risk characterisation	Hazard conclusion (see section 7)
Freshwater	Qualitative	PEClocal value estimation Chesar 3.4
Sediment (freshwater)	Qualitative	PEClocal value estimation Chesar 3.4
Marine water	Qualitative	PEClocal value estimation Chesar 3.4
Sediment (marine water)	Qualitative	PEClocal value estimation Chesar 3.4
Sewage treatment plant	Qualitative	PEClocal value estimation Chesar 3.4
Air	Qualitative	No hazard identified
Agricultural soil	Qualitative	PEClocal value estimation Chesar 3.4
Predator	Not required	No hazard identified

Comments on assessment approach:

A mass balance approach that accounts for all quantities of 4-tert-OPnEO has been utilized throughout the CSR. As a worst-case scenario, it is assumed that all quantities of 4-tert-OPnEO supplied to the downstream users (in reagents) are released to the wastewater stream as 4-tert-OPnEO where it will be converted in the STP and released to the environment as 4-tert-OP.

In accordance with the "Risk-related considerations in applications for authorisation for endocrine disrupting substances for the environment, specifically OPnEO and NPnEO" which was agreed at EU REACH RAC 43, Applicants as "a worst-case, can assume that all 4-tert-OPnEO released to the environment will eventually be present as 4-tert-OP". In the case of this CSR, the Applicant assumed that all 4-tert-OPnEO breaks down to 4-tert-OP during residence in the STP. Please note that input parameters used in CHESAR are for 4-tert-OP, on which the risk assessment is based. This represents a very conservative approach and worst-case scenario.

A conversion factor of 0.33 is applied to quantities of 4-tert-OPnEO released to the environment in order to express releases in terms of 4-tert-OP. The conversion factor was calculated based on the relative molecular weights of 4-tert-OP (MW = 206.3) and 4-tert-OPnEO with an average of 9.5 ethoxylate units (MW = 625). The Applicant's total tonnage includes a smaller quantity (4% of total) of highly ethoxylated (n=35) 4-tert-OPnEO used only in part of the reagent formulation use. A single conversion factor of 0.33 based on 4-tert-OPnEO with an average of 9.5 ethoxylate units is applied, as a worst-case, to the total tonnage in order to have representative analysis.

The following substance properties are used in the environmental fate estimation completed by EUSES. They correspond to the "value used for CSA" reported in sections 1 and 4 of the CSR. Please note that these values are for 4-tert-OP, on which the risk assessment is based. Values for 4-tert OP10EO are also listed for comparative purposes to illustrate differences in the modelled distributions in the biological sewage treatment plant.

Table 9.0.3: Key physicochemical property data used in the assessment for 4-tert-octylphenol

Substance property	4-tert-OP	4-tert-OP10EO
Molecular weight used for the assessment	206.3	646.9
Vapour pressure	0.001k Pa at 20 °C	$0.24 \cdot 10^{-11}$ Pa
Partition coefficient (Log Kow)	4.8 at 22 °C	2.39 at 20 °C
Water solubility	19 mg/L at 22 °C	189 mg/l at 20 °C (critical micellar concentration)
Melting point	84.5°C	Not available
Boiling point	289°C, at 101kPa	Not available
Biodegradation in water: screening tests	inherently biodegradable	inherently biodegradable
Bioaccumulation: BCF (aquatic species)	740 dimensionless	Not available
Adsorption/Desorption: Koc at 20 °C	10,000	18.20

In a standard (modelled) biological STP, the emissions are distributed as shown in Table 9.0.4.

Table 9.0.4: Fate (release percentage) in the modelled biological sewage treatment plant

Release to water	43.0%	98.7%
Release to air	4.8%	1.1%
Release to sludge	52.2%	0.2%
Release degraded	0%	0%

The above fractions are calculated by the SimpleTreat model integrated in EUSES. They are calculated for 4-tert-OP, with the assumption that all 4-tert-OPnEO will be converted to 4-tert-OP in the STP and distribution to different compartments is based on 4-tert-OP's physicochemical properties.

For comparison, the SimpleTreat model was also run for 4-tert-OP10EO, which is closest to the average ethoxylation for the 4-tert-OPnEO used by the Applicant (average n = 9.5), with an assumption of no degradation in the STP. The model predicts that the substance would be present almost exclusively in the liquid outflow of the STP, mainly due to the very low adsorption / desorption coefficient (Koc). In practice, the situation is expected to be somewhere between these two extremes, with only partial degradation to 4-tert-OP occurring in the STP. The degradation products, according to information in the Annex XV dossier (BAuA, 2012), would most likely be 4-tert-OP1/2EO, 4-tert-OPnEOs and 4-tert-OP. Their distribution to water, air and sludge varies. All these degradation products are expected to degrade to 4-tert-OP over time. The current approach in the CSR is carrying out the analysis using the values for 4-tert-OP. Estimated releases of 4-tert-OPnEO to agricultural soil via application of sludge from STPs are likely to be higher than actual, while estimated releases to surface water and sediment may be lower.

Overall, the approach to assessing environmental exposure will be qualitative since there is still scientific debate about whether thresholds exist for endocrine disruption and therefore whether any derived PNEC values would be accepted. The assessment will show that the releases of 4-tert-OPnEO are as low as technically possible. This will be complemented by a demonstration of the risk management measures taken by the Applicant to minimise exposure to as low as technically and practically possible and to show that releases to the environment will decrease quickly and substantially after the sunset date due to the Applicant's substitution activities.

The hierarchy of control principles have been followed with the Applicant's implementation of their ongoing substitution plan as detailed in the Analysis of Alternatives and as noted in the conclusions on risk management. The hierarchy of control is a widely accepted system where control methods at the top of hierarchy are potentially more effective and protective than those at the bottom. Following this hierarchy normally leads to the implementation of inherently safer systems, where the risk of illness or injury or release has been substantially reduced. The Control of Substances Hazardous to Health Regulations 2002 (SI 2002/2677) (as amended) Regulation 7, defines occupational 'hierarchy of control' in order of priority from the top down as: 1). Elimination or substitution, 2). Engineering controls, 3). Collective protection measures and 4). Individual protection measures. Though generally considered a safety and health concept, the same principles can be considered for environmental control strategies with substitution at the top of a hierarchy for environmental risk management.

9.0.2.2 Man via environment

Scope and type of assessment:

The scope of this assessment focuses on the environmental exposure only. Type of risk characterisation required for human health exposures is not evaluated in this application as the substance has been placed onto UK REACH (The REACH etc. (Amendment etc.) (EU Exit) Regulations 2019; SI 2019 No. 758) on the basis of its endocrine disrupting properties in environmental species. In accordance with existing ECHA Guidance Document R.16 on Environmental Exposure Assessment: "An assessment of indirect exposure of humans via the environment is generally only conducted if: a) the tonnage is >1,000 t/y or b) the tonnage >100 t/y and the substance is classified b1) as STOT RE 1; or b2) as a carcinogen or mutagen (any category); or b3) as toxic to reproduction (categories 1A or 1B)" (ECHA, 2016 Pg 25). The substance 4-tert-OPnEO is used by the Applicant at between 10 and 100 t/y and is not classified for any of the mentioned hazard categories. As human health hazards are not relevant to this application for authorisation, an assessment of secondary exposure of man via environment is not considered necessary.

9.0.2.3 Workers

Scope and type of assessment:

The scope of this assessment focuses on the environmental exposure only. Risk characterisation required for workers is not evaluated in this application as the substance has been placed onto UK REACH (The REACH etc. (Amendment etc.) (EU Exit) Regulations 2019; SI 2019 No. 758) on the basis of its endocrine disrupting properties in environmental species and thus only its effects and impacts on the environment are of relevance. Worker exposure is not relevant for this application as determined in the Annex XV dossier (BAuA, 2012).

Comments on assessment approach related to toxicological hazard:

Not relevant - worker hazards are not subject to assessment in this CSR.

Comments on assessment approach related to physicochemical hazard:

Not relevant - physicochemical hazards are not subject to assessment in this CSR.

General information on risk management related to toxicological/environmental hazard:

The Risk management measures (RMM) related to the control and prevention of releases to the environment are specific to each use and as a result are outlined in the individual Use 1 Exposure Scenarios described below.

9.0.2.4 Consumers

Scope and type of assessment:

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

9.1 Exposure Scenario 1 for the environment: Professional use as a surfactant in the final use of *In-Vitro* Diagnostic Devices (IVDs) for clinical testing using ARCHITECT, Alinity and ABBOTT PRISM automated analyser systems

Environment contributing scenario(s): ERC 8a: Widespread use of non-reactive processing aid (no inclusion into or onto article, indoor)

Sector of Use: SU20 Health Services

Products Category: PC21: Laboratory Chemicals

Worker/Consumer contributing scenario(s): PROC 0: Other - Use in IVD Instruments with controlled exposures

Technical function of the substance: Surfactant

* Exposure Scenario 1 involves the professional use of reagents containing 4-tert-OPnEO in the final use of the IVDs. The only manual step is the loading and unloading of open/closed containers with the reagents onto enclosed automated analyser systems (PROC 0).

Explanation on the activities and technical processes covered in the exposure scenario:

4-tert-OPnEO is present in some of the reagents used by the Applicant's customers. These reagents are used in core laboratory immunoassay, clinical chemistry and blood transfusion products. Reagents are used in all of the Applicant's instruments (ARCHITECT *i*, Alinity i, ARCHITECT *c*, Alinity c, Alinity s, and ABBOTT PRISM).

The Applicant supplies the reagents in either individual bottles or as cartridges fixed on a rigid frame, so they are loaded together on the instrument.

The bottles and cartridges are loaded and unloaded manually. This is the only routine manual task involving the reagent solutions containing 4-tert-OPnEO. All other operations are carried out automatically by the instrument. Each instrument will in order:

- Use pipettors to aspirate the required quantities for each test from the bottles and to dispense in the reaction vessels (for immunoassays) and in the cuvettes (for clinical chemistry) on the processing centre.
- Mixes reagents with samples and allows the solution to incubate at controlled temperature.
- After processing is over and the sample has been analysed, the contents of the reaction vessel / cuvette are discarded. Cuvettes are washed to remove leftover material, while the reaction vessels are discarded into solid waste. After testing is complete, the content of the reaction vessel is aspirated and discharged to liquid waste.

There is no manual intervention in the processing of the samples and all work is carried out in an enclosed area. Figure 1 outlines the steps required to produce a test result using the ARCHITECT *i* system.

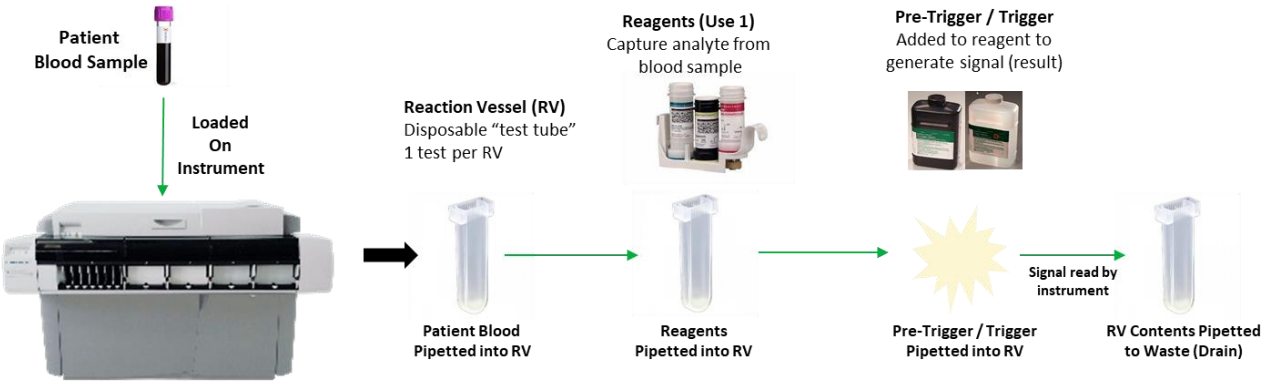

Figure 1: Steps required to produce a test result using the Applicant's ARCHITECT i system.

ABBOTT PRISM instruments do not have a liquid waste stream. They have a different design, in which the test reaction takes place on the surface of a glass fibre filter contained in a reaction tray. Sample and reagents used in the tests are retained in a reaction tray which contains an absorbent material, as shown in Figure 2 below.

Each tray can process 16 tests. After the tests have been completed, the trays are ejected from the instrument into the solid waste container and sent for treatment as solid biohazardous waste. GB ABBOTT PRISM customers dispose of this waste by incineration.

Figure 2: ABBOTT PRISM immunoassay tests are performed on reaction trays.

Explanation on the approach taken for the ES:

Water

The downstream use of the Applicant's products is considered to be widely dispersive in nature since it occurs at over 130 customer locations across GB. These sites are spread all over GB and vary in the level of IVD kit usage from a small number of tests per day to greater than 10,000 – 100,000 ([redacted]) tests per day for the higher volume users. For the assessment, the daily wide-dispersive use was estimated from the total annual usage for all downstream users in GB following ECHA Guidance R16 (ECHA, 2016). The total annual tonnage usage for all downstream users (laboratories / hospitals / blood banks, etc.) in GB was calculated as described above in section 9.0.1.

To verify the validity of a wide-dispersive use assessment, specific use information was collected for four downstream user local areas. Based on ECHA's R16 guidance, (section R16.1.4.1) the customer releases were grouped together (as applicable), based on their city/town location and proximity to each other resulting in an aggregate value for each location. Grouping of the customers is based on the expectation that all customer releases will enter the same sewage treatment plants, and hence, the same water bodies if they are in the same city/town (herein referred to as local areas), thus contributing to the overall environmental concentration.

The four local areas cover a range of release rates, categorized as very high, high, medium, and low. Calculated environmental concentrations were based on test usage, amount of 4-tert-OPnEO per test, STP capacity and receiving body of water flow rate and other relevant available information.

An instrument data analytics system, AbbottLink, was used to capture specific use information (number of tests run) for the downstream users in four example local areas.

For the estimation of 2021 release rates for the four local areas, year-to-date testing data was obtained from the AbbottLink system on 19 May 2021. This provided the total number of all immunoassay (IA) and clinical chemistry (CC) tests performed at each customer site. The number of tests performed during the 139 day period captured in the data pull was annualised, the average number of tests per day was calculated and from that the average daily releases were estimated. While typical downstream user sites run testing 7 days per week, the number of tests run on weekdays is greater than the number of tests run on weekend days. Therefore, simply dividing the annual test volume by 365 days resulted in an average daily test volume that underestimated the average weekday test volume. A suitable denominator (other than 365 days) was chosen to arrive at an average daily test volume that was close to the typical weekday test volume. A denominator value of 275 was used for immunoassays (IA) and 296 for clinical chemistry

(CC). As the data for both IA and CC were combined, the average of the two values (286) was selected for the number of operational days.

The daily wide-dispersive use calculation as described by R.16 guidance (ECHA, 2016).

According to R.16.2.2.1.2. Estimation of tonnage for widespread uses, a default daily amount used in a standard town is estimated starting from the tonnage for the use, and taking into account:

- the fraction of the "tonnage for the use" used in the region (regional tonnage),
- the fraction of the regional tonnage used in the standard town (proportional to the ratio of number of inhabitants in a standard town (10 000) compared to the number of inhabitants in a region (20 000 000)),
- the number of days in a year: 365
- The resulting tonnage is multiplied by an assessment factor of 4 to take into account geographical or temporal peaks in the use of a substance.

The daily wide-dispersive use calculation for this assessment

For the purpose of this assessment, the daily wide-dispersive use was estimated per site starting from the total annual usage for GB and dividing it by:

• 10: Fraction of the total tonnage at EEA level used in the region,
• 2'000: Fraction of the regional tonnage used in the standard town of 10'000 inhabitants (versus 20'000'000 inhabitants in the region),
• 286 (day/a): number of operating days (see detailed explanation above on number of operational days) in a year defined per product group and multiplying it by a safety factor of 4 to take into account geographical or temporal variations in the use and releases as recommended in Guidance R16 (ECHA, 2016).

Daily amount (kg/day) = total annual usage for all GB customers × 4 / (10×2000×286 days) as determined in the Guidance R16 (ECHA, 2016). This release rate was subsequently used to determine wide dispersive daily release rate of 1.0 x 10^{-5} - 1.0 x 10^{-4} kg ([redacted] kg) in CHESAR.

Table 9.1.1 Exposure scenario for ES1, name and related environmental contributing scenarios

#	Exposure scenario (ES) name and related environmental contributing scenarios	Wide dispersive usage (t/year) *	Daily local usage for wide dispersive use (t/day)
ES1 (PW)	Wide dispersive use standard approach	0.01 – 0.1 [redacted]	
	Wide dispersive use standard approach (ERC 8a)		1.0E-8 – 1.0E-7 [redacted]

*Wide dispersive use quantity for the ES assessment does not include ABBOTT PRISM concentrations as these quantities are collected and are incinerated.

The daily use for the four local areas was calculated as follows:

The average daily releases were calculated by multiplying the average daily test volumes by the average quantity of 4-tert-OPnEO per test estimated in the Applicant's EU REACH CSR. The average quantity of 4-tert-OPnEO per IA test was calculated from the total quantity of 4-tert-OPnEO used by the Applicant to produce immunoassay reagents divided by the total number of tests produced. The average content of 4-tert-OPnEO per immunoassay test was determined to be 0.1 – 1 mg ([redacted] mg). For clinical chemistry, the average quantity per test of 0.1 – 1 mg ([redacted] mg) was calculated from the i) volume of reagents sold in the EEA, ii) the concentration of 4-tert-OPnEO in the reagents and iii) the number of tests sold in the EEA.

According to ECHA's guidance, section R.16.1.4.1. for local assessment, "The concentrations of substances released

from a single point source (industrial site or standard municipal biological STP) are to be assessed after release to the environment. The exposure targets are assumed to be exposed at the vicinity of the release point. In general, concentrations are calculated on the basis of a realistic daily release rate" (ECHA, 2016 p.28). In addition, considerations for widespread uses are also outlined in R16.1.4.1; "Widespread uses are usually assumed to occur in an urban infrastructure. The assumption is that the substance is used by consumers or by many users in the public domain, including small, non-industrial companies. Releases to water are assumed to be collected in a central public sewage system and are then treated by a biological STP. Since the releases to water from all the widespread uses can, by default, be assumed to enter into the same sewage system, combined risk from all the widespread uses has been considered". (ECHA, 2016 p.30)

The four example local areas represent very high, high, medium and low release categories based on their daily release rates. The cut-off points of each of the other emission categories was selected to be approximately one order of magnitude lower than the cut-off point of the previous (higher) emission category based on the daily release quantities, i.e. $1/10^{th}$ of the higher cut-off point.

Table 9.1.2 Overview of Emission Categories

Emissions Category	Daily emissions range (kg)
Very High	> 0.00400
High	> 0.00100 to ≤ 0.00400
Medium	> 0.00010 to ≤ 0.00100
Low	≤ 0.00010

Environmental exposure is influenced by various conditions such as substance properties, release rates, characteristics of biological STPs, tonnage and time patterns of release as outlined in R16 Guidance Table 16-6 (ECHA, 2016). The substance properties are already defined in accordance with the data provided in the Annex XV dossiers for 4-tert-OPnEO and 4-tert-OP (Table 9.0.3) (BAuA, 2012). In the absence of any site-specific information, default values are recommended and represent a conservative estimation. However, as customer site specific data is available from AbbottLink, further refinement within each category was undertaken to take into consideration the impact of such environmental conditions on the release rates.

The four local areas were included as they cover the range of release profiles within the Applicant's downstream users. These local areas were assessed to supplement the wide dispersive use method of calculation. The following strategy was implemented.

- From each usage category (very high, high, medium, low), one local area was selected.
- Where more than one customer was present in a local area, these values were aggregated to allow for the assumption that these will enter the same sewage treatment plants, and hence, the same water bodies if they are in the same city/town
- Discharge rates and receiving water have significant influences on emission characteristics. In order to account for this the initial list for each usage category was screened manually to ensure sites would provide varying combinations of size of STP (i.e. high, medium, low) and type and size of the receiving body of water (i.e. high, medium, low, coastal (marine)).
- This strategy was chosen to have a site sample selection that covered a range of release values, environmental scenarios and geographical distribution to evaluate the emission characteristics of the downstream users, and to complement the wide dispersive use calculation. The approach for assessment of these factors is discussed in more detail in the following sections.

Overall, it is considered that the selection of the four local areas is representative of the different environmental scenarios of the Applicant's downstream users of 4-tert-OPnEO, concerning emission profile, receiving STP size, geographical location and flowrate of receiving water bodies.

Table 9.1.3 Tonnages used for site specific (local areas) assessment.

No.	Local Area examples	Daily local tonnage (OPnEO tonnes/day)	Annual local tonnage (OPnEO tonnes/year)
1	Site 1	1.00E-5 – 1.00E-4 a	1.00E-3 – 1.00E-2 a
2	Site 2	1.00E-5 – 1.00E-4 a	1.00E-3 – 1.00E-2 a
3	Site 3	1.00E-7 – 1.00E-6 a	1.00E-4 – 1.00E-3 a
4	Site 4	1.00E-7 – 1.00E-6 a	1.00E-5 – 1.00E-4 a

Receiving body of water

Receiving body of water dilution rates can impact the final concentration of 4-tert-OP to the environment. Larger rivers, for example the Thames, have a very high flow (over 1,000,000 m^3/day), which dilutes concentration of 4-tert-OP much more than a smaller river with low river flow. The population size and the water flow of the receiving body of water together account for the overall dilution achieved in the wastewater. The model used by Chesar assumes a default dilution factor of 10 and it is suggested that the maximum dilution factor used with the model is 1000. These two values can be used to define the worst-case and best-case environmental concentrations with the quantities of 4-tert-OPnEO used. The receiving body of water was determined for each of the selected local areas, based on the location of the selected STP and the identification of the discharge point. One third of the average flow rate value was used, as per the suggestion of ECHA's R16 Guidance Document (Appendix A.16-3.3.3) (ECHA, 2016). If there was no information on flow rate or tidal churn, default dilution factors of 10 (river) and 100 (coastal) were selected. River flow rates for each site were taken from the European Commission project SWITCH-ON for river flows, available online at: https://cordis.europa.eu/project/rcn/110496/reporting/en or from relevant sources of information on the local areas receiving water bodies.

Sewage treatment plant analysis

Treatment of wastewater in sewage treatment plants is also known to affect expected environmental concentrations of 4-tert-OPnEO. The four selected local areas represented a range of STP sizes. The default STP in ECHA's guidance on environmental exposure assessment is for a town with population of 10,000. A small minority of the Applicant's customers are high-usage customers located in larger GB cities , served by multiple, larger STPs (e.g. p.eq 500,000+) than would be found in smaller cities. This in turn could lead to a higher dilution factor which would significantly change the emissions estimates for these high-volume locations.

The relevant discharge rate was determined for the STP for each of the four selected areas. The STP information for each location was taken from the European Environment Agency's (EEA) Interactive Urban Wastewater Treatment Map (Urban Waste Water Treatment Map, accessed 2021). Details of the STP, such as STP generated load (in p.eq.) and the daily volume of treated wastewater were collected. Average or dry weather flowrates were used in these cases. If data were not available, a default value of 200 L per p.eq. was used, according to ECHA's R16 Guidance Document (ECHA, 2016). This parameter can affect the dilution of the liquid waste stream containing 4-tert-OPnEO until it reaches the STP. ECHA's guidance document R16 suggests a default of 200 L per person of wastewater generated daily. Larger communities will generate more wastewater, so local concentrations of 4-tert-OPnEO will be lower. This can also be approximated by the dry liquid outflow of the STP, which indicates a lower limit of wastewater.

The information relating to the local areas is shown in Appendix II. The values were used in the calculations of the site-specific assessment carried out in Chesar 3.4, using the built-in EUSES 2.1.2 model. The exercise was carried out to only determine the contribution of 4-tert-OPnEO in the Applicant's reagents to local environmental concentrations.

STP locations and discharge points were identified using the European Environment Agency's (EEA) Interactive Urban Waste Water Treatment Map (European Environment Agency, 2021). At local areas where there was only a

single STP serving the area, that single STP was selected. Multiple STP locations are more commonly found in large cities while smaller regional towns and cities were usually represented by a single STP. However in this assessment, a worst-case assumption was taken, and only one STP was chosen where there may have been multiple STPs (assuming all emissions from one local area enter the single STP).

Solid Waste

4-tert-OPnEO that is contained in the reagents is also used with ABBOTT PRISM instruments. The immunoassay tests performed by the instrument occur in a reaction tray that retains all the patient sample and required reagents in an absorbent material following completion of the test. The used trays are considered biohazardous biological waste as per the recommendations in the operational manuals.

Liquid waste from unused reagents, empty containers and solid biohazardous waste are disposed of by collection and incineration as confirmed with the single GB ABBOTT PRISM customer. There are no releases of 4-tert-OPnEO to the environment arising from ABBOTT PRISM use, therefore the ABBOTT PRISM usage quantity of 10-100 *a* kg is not included in the exposure assessment.

9.1.1 Environmental contributing scenario 1

9.1.1.1 Conditions of use

Product (article) characteristics
Physical form of substance: Liquid Substance in preparation: No
Amount used, frequency and duration of use (or from service life)
Daily use amount at site (Wide dispersive use): <= a tonnes/day *Based on a wide dispersive use approach, assuming an estimation of tonnage applied to a default daily amount in a standard town (Standard wide dispersive use, R16 guidance, R16.2.2.1.2).*
Annual use amount: <= a tonnes/year *Based on 2021 data of total usage for ES1*
After implementation of risk management measures, emissions subject to release to wastewater: <= 0.093 tonnes/year *Based on 2021 data on the total annual emissions from all sites*
Frequency and duration of use: Number of emission days per year: 286 days (average of 275 Days for Immunoassay and 296 days for Clinical Chemistry). Further explanation has been provided above.
Percentage of total EU tonnage used at regional scale: 10%
Technical and organisational conditions and measures
▪ N/A
Conditions and measures related to sewage treatment plant
▪ Biological STP: Standard [Effectiveness Water: 56.99%] *Calculated by the SimpleTreat model embedded in Chesar*
• Discharge rate of STP: 2,000 m^3/day (standard wide dispersive values, R.16 guidance)
▪ Application of the STP sludge on agricultural soil: Yes (standard wide dispersive values, R.16 guidance)
Conditions and measures related to treatment of waste (including article waste)
▪ Particular considerations on the waste treatment operations: No *Waste disposal according to national/local legislation is sufficient*
Other conditions affecting environmental exposure
▪ Receiving surface water flow rate: 18,000 m^3/day (standard wide dispersive values, R.16 guidance)
Additional good practice advice. Obligations according to Article 37(4) of REACH do not apply
▪ N/A

9.1.1.2 Releases

Table 9.1.4 Local releases to the environment

Release	Release factor estimation method	Explanation / Justification
Water	Measured Release Rates	**Initial release factor:** 10-100 ([b]) % **Final release factor:** 10-100 ([b])% **Local release rate:** WDU: 6.5 x 10^{-5} OPnEO kg/day (2.2 x 10^{-5} OP kg/day) Releases per the four example local areas are presented in Appendix II. **Explanation / Justification:** A conversion factor 0.33 is applied to the initial release factor (of 4-tert-OPnEO) to adjust the final release factor and local release rate (expressed as 4-tert-OP). All quantities 4-tert-OPnEO in reagent solutions are assumed to be released directly to the facility's wastewater system and from there to the local municipal sewage system. Based on information from the Applicant's instrument data analytics system, AbbottLink, and the average content of 4-tert-OPnEO in reagents per test 0.1-1 mg ([c]) for immunoassays and 0.1-1 mg ([c]) per test for clinical chemistry).
Air	ERC Release Rates	**Initial release factor:** 0% **Final release factor:** 0 % **Local release rate:** 0 kg/day **Explanation / Justification:** The substance is not volatile and all operations take place at low temperatures. The reagent carrousel is cooled at a temperature of 7°C, with a range of 2-12°C. The vapour pressure of 4-tert-OPnEO at 20°C is practically zero ($0.24 \cdot 10^{-11}$ Pa). Furthermore, all operations involving 4-tert-OPnEO are in an enclosed instrument, so, until release to the drain, the substance is never in the open. Therefore, no releases to air are assumed.
Soil	ERC Release Rates	**Final release factor:** 0% **Explanation / Justification:** All DU use operations are conducted in enclosed instruments which are directly connected to drain with no direct release to soil

Releases to waste

Water

Reagent solutions are used in clinical chemistry and immunoassay (core laboratory and transfusion) tests across GB.

The users of the clinical chemistry and immunoassay IVD kits are hospitals, clinics, medical labs and blood banks. There are over 130 individual users in GB and it was not possible to determine how each individual user deals with their liquid waste containing 4-tert-OPnEO.

System operations manuals provide recommendations for waste handling, stating that each facility is responsible for labelling all waste containers and characterizing its waste stream to ensure waste is disposed of in accordance with the appropriate local, state, and national regulations.

It is possible that small quantities of Architect & Alinity reagent solutions remain in the bottles and cartridges when these are replaced. The empty containers are disposed of as solid waste. The main options of handling solid waste are

landfilling and incineration. If the plastic bottles are incinerated, all quantities of 4-tert-OPnEO present in them will be destroyed. In case of landfilling, there is potential for release. However, the substance is not volatile, so no emissions to air are expected. Only possible emission route is from leaching in landfills. The leachate may be led to a biogas generating facility at the landfill site or it may reach nearby water bodies. In either case, only chance of releases will be to water.

As a conservative approach, it is assumed that all quantities of 4-tert-OPnEO included in reagents are used for testing and are discharged to the local municipal sewage systems. The release factor to the environment wastewater is assumed to be 100%.

Solid Waste

4-tert-OPnEO that is contained in the reagents is also used with ABBOTT PRISM instruments (10 – 100 a kgs/year OPnEO). The immunoassay tests performed by the instrument occur in a reaction tray that retains all the patient sample and required reagents in an absorbent material following completion of the test. The used trays are considered biohazardous biological waste as per the recommendations in the operational manuals and are incinerated. All ABBOTT PRISM waste (including residuals in the supplied bottled and the bottles themselves) are incinerated, there are no emissions to the environment therefore no further assessment for ABBOTT PRISM quantities were conducted.

Table 9.1.5 Summary of 4-tert-OPnEO used and released expressed as 4-tert-OP (based on 2021 quantities)

Use 1	Total 4-tert-OPnEO kg/year used	Total 4-tert-OPnEO kg/year released	Total 4-tert-OP kg/year released
Total	10-100 (a)	93	30.69

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

Water: The following table provides Local (Clocal) emissions and Predicted Environmental Concentrations (PEC) for the four-example downstream user site locations and, for comparison, the wide dispersive use as evaluated for ES 1. Detailed information on the emissions for each individual location are reported in Appendix II.

Table 9.1.6 Clocal and PEC emission concentrations for emission categories within local areas & the wide dispersive use assessment

Table 9.1.6: Clocal and PEC emission concentrations for emission categories within local areas and the wide dispersive use assessment

Assessment	WDU		1		2		3		4	
Emission category	NA		Very high		High		Medium		Low	
Exposure assessment	Clocal	PEC	Clocal	PEC	Clocal	PEC	Clocal	PEC	Clocal	PEC
Freshwater mg/L	4.54E-07	4.74E-07	2.44E-06	2.46E-06	1.72E-06	1.74E-06	NA	NA	2.45E-07	2.64E-07
Sediment (freshwater) mg/kg dw*		4.76E-04		2.47E-03		1.75E-03		NA		2.65E-04
Marine water mg/L	4.54E-08	4.77E-08	NA	NA	NA	NA	1.46E-08	1.68E-08	NA	NA
Sediment (marine water) mg/kg/dw*		4.79E-05		NA		NA		1.69E-05		NA
Sewage treatment plant mg/L		4.61E-06		3.23E-05		3.34E-05		1.48E-06		8.47E-07
Air mg/m^3	2.86E-10	3.12E-09	5.78E-06	5.78E-06	2.24E-06	2.24E-06	8.68E-08	8.97E-08	8.28E-10	3.69E-09
Agricultural soil mg/m^3	1.44E-04	1.44E-04	1.07E-03	1.07E-03	1.07E-03	1.07E-03	4.70E-05	4.71E-05	2.64E-05	2.66E-05

*For sediments, EUSES does not return a local concentration (without regional contribution) and thus no estimate is available (Guidance Chesar 2, Section 25.3)

Remarks on measured exposure:

Releases from the downstream use of the Applicant's IVD reagents occur through the discharge of the IVD analyser liquid waste to the local area wastewater treatment plants. Use of the IVD reagents is widely distributed in hospitals, clinical labs, and blood screening centres across GB. As this is considered a widespread use, the Applicant examined a wide dispersive use calculation and verified this value against four example exposure scenarios. The widespread use assessment was carried out, as described in 9.1, and resulted in a predicted environmental concentration (PEC) of $4.74E^{-7}$ OP mg/L for the freshwater compartment, and $4.77E^{-8}$ OP mg/L for the marine compartment.

To review this situation, the Applicant evaluated a subset of their downstream user profiles (very high, high, medium, low emissions), receiving STPs and different environmental compartments. The range of these four examples resulted in a lowest predicted concentration of $2.64E^{-7}$ OP mg/L for freshwater (local area #4), $1.68E^{-8}$ OP mg/L for marine water (local area #3), and highest predicted concentration of $2.46E^{-6}$ OP mg/L for freshwater (local area #1).

As can be observed by the information in Table 9.1.6, the resulting local concentrations and PECs for fresh and marine water are very low, in the range of ng/l or below.

The four local areas assessed illustrate the range of release rates expected for the downstream use where; resulting Clocal and PEC across GB would be expected to vary depending on the particulars of individual STPs and receiving bodies of water. The highest concentrations of emissions can be expected to be seen in areas that have higher usage such as large capital cities, with receiving water bodies that may not have high dilution rates (moderately flowing rivers). Higher concentrations could also be expected in medium usage local areas where waste is received by a small STP that discharges to rivers with low flow rates (low dilution). It should be noted that, in selecting these local areas and the parameters to use for the calculation of the environmental concentrations, conservative approaches were used. More specifically, a single STP was used for the very high-volume local area (local area #1), where it is more reasonable to assume that treatment of waste is spread over several STPs. A single STP was selected as a worst-case assumption, as it leads to lower dilution and higher environmental concentrations.

Through both methods of calculations, local areas with specific individual data, or through wide dispersive use calculation, the predicated environmental concentrations are either within the same order of magnitude (Local areas #3 & #4 and WDU measuring E^{-7} OP mg/L), or one order of magnitude higher (Local areas #1 & #2 measuring E^{-6} OP mg/L). As a result of this assessment, it can be assumed that the predicated environmental concentrations reflected through the wide dispersive use assessment exposure scenario for ES1 are broadly accurate, given the variation in the Applicant's downstream user profiles and therefore was considered to be an appropriate value for use in the overall exposure assessment.

Conclusion on risk characterisation:

Risk Management and Controls

Based on hierarchy of control principles the following risk management measures were considered.

Substitution plan

The Applicant, as described in the Applicant's Analysis of Alternatives, is carrying out a large R&D project, aiming at full substitution of 4-tert-OPnEO from all reagents in immunoassay and clinical chemistry IVD kits.

Due to the large number of affected IVD assays and the requirement to receive regulatory approval for each individual product, it is not possible to substitute 4-tert-OPnEO in all reagents by the Sunset Date. The Applicant prioritised substitution of the product that accounted for 90% of the total 4-tert-OPnEO releases. This product (Trigger) launched in GB in 2020 and is therefore not included in the exposure assessment. The Applicant has a staggered substitution plan for the remaining assays, which will gradually reduce the number of IVD kits that contain 4-tert-OPnEO and the releases of the substance to the environment in GB.

Considerable resources have been allocated to REACH remediation activities by the Applicant, with funding of £10-100 (£[redacted] million. This is the cost associated with the substitution activities required for approximately 200 products. As discussed in the SEA, the substitution effort was initiated due to the EU REACH regulation. As the GB sales are 1-25% ([redacted]) of the Applicant's EU sales, the cost of substitution used for this analysis will be proportional or £1-10 million (£[redacted] million). The Applicant is applying all available resources to prioritize and expedite substitution of 4-tert OPnEO and other SVHCs in all products.

Minimisation of releases and feasibility

Based on available technology, collection and incineration of waste is the only treatment method available to eliminate releases of 4-tert-OPnEO from the instrument effluent. However, prevention of release to the environment through collection and incineration is not possible at hospital, blood screening and clinical laboratories due to space and infrastructure limitations.

It is important to note when considering the feasibility of controlling releases of 4-tert-OPnEO from IVD kit reagent usage at downstream user sites that concentrations in liquid waste are very low (maximum of 0.0001 – 0.001 (l) % directly at the outflow of the analyser in 2021). Therefore, the volume of wastewater will be extremely high relative to the quantity of 4-tert-OPnEO. As a result, local regulations governing disposal generally allow the instrument effluent to be disposed of as non-hazardous wastewater. A standard core laboratory immunoassay analyser will generate approximately 5.5 L of liquid waste per hour, while a clinical chemistry analyser will produce between 15 – 53 L per hour depending on the system and throughput. Given this high volume of liquid waste generated, the analysers in place at downstream user sites are generally plumbed directly to the wastewater drain.

A typical customer will have several such devices that are plumbed directly to drain. Extensive infrastructural upgrades would be required to re-route drainage systems and divert the analyser waste from other facility wastewater. This could involve internal excavation work and navigation through wards, cleanrooms, and other controlled areas. Even if separate drainage systems could be established, in reasonable time and at reasonable cost (which in general we believe is not possible), then it would require large scale collection tanks to be installed externally, with secondary containment and enough room for a tanker lorry to maneuver to make regular wastewater collections. External space considerations would then come into play which again shows the practical infeasibility of waste collection. Hospitals are often limited in external (as well as internal) space.

Some larger customers may have waste treatment incineration facilities on site; however, the capacity of local liquid waste treatment is generally 200kg/d to 1t/d at the very maximum (WHO 2016, Addfield Environmental Systems 2021). A single large-scale analyser would therefore generate more waste than the incineration capacity available at even the larger customer sites.

The Applicant is implementing comparable analyser waste containment projects at EU manufacturing sites which will result in temporary disruption to QC testing activities. While this can be accommodated at a manufacturing facility, for example by proactively building inventory to bridge the shutdown period, it is not possible for a clinical laboratory to cease testing without jeopardizing patient care and safety. Downstream users within scope of authorisation cumulatively perform 10-100 million (e million) individual immunoassay and 100-1,000 million (e million) clinical chemistry tests annually across GB using the Applicant's immunoassay and clinical chemistry systems. Workflow disruption during facility modifications would lead to a delay in generating and reporting test results, which in turn would lead to delayed diagnosis and adverse patient outcomes.

Technical Feasibility of Alternatives to Collection and Incineration: The logistical aspects of collection and incineration demonstrate the infeasibility of these measures. Accordingly, the Applicant has evaluated the technical feasibility of various treatment technologies that might be deployed at customer sites as an alternative to collection and incineration.

There are no commercially available treatment technologies with proven efficacy in reducing/preventing 4-tert-OPnEO from the analyser liquid waste stream. The Applicant has evaluated two technologies to determine their capability and determined they are not practical/feasible.

Advanced Oxidation Processes: h

h

h [redacted]

Activated Carbon Filtration: h [redacted]

None of these alternatives have proven to be a viable alternative to incineration. Therefore, the entire quantity of 10 – 100 (g) million litres of wastewater would have to be collected and incinerated annually to prevent 4-tert-OPnEO releases from Use 1.

Economic feasibility: As shown in Table 9.1.7, over 10 – 100 (g) million litres of wastewater would have to be collected and incinerated annually to prevent 4-tert-OPnEO releases from Use 1. The cost effectiveness would decrease significantly over time. Analyser liquid waste volume will remain constant, whereas the 4-tert-OPnEO concentration will reduce over time as individual products are substituted. The net result is that the incineration cost to prevent 1 kg 4-tert-OPnEO release rises over the review period, exceeding 1-10 (d) million-pound sterling per kg in 2027. These figures exclude facility modification costs which are expected to far exceed the annual incineration costs.

Table 9.1.7: Annual cost to incinerate liquid waste to prevent 1 kg 4-tert-OPnEO release from downstream users

Year	kg 4-tert-OPnEO per year	Liquid waste volume (L)	Volume of waste to prevent 1 kg 4-tert-OPnEO release (L)	Incineration cost to prevent 1 kg 4-tert-OPnEO release (£)	Incineration cost discounted to 2021 prices (£)
2022	44	g [redacted]	g [redacted]	d [redacted]	d [redacted]
2023	81	g [redacted]	g [redacted]	d [redacted]	d [redacted]
2024	57	g [redacted]	g [redacted]	d [redacted]	d [redacted]
2025	21	g [redacted]	g [redacted]	d [redacted]	d [redacted]
2026	15	g [redacted]	g [redacted]	d [redacted]	d [redacted]
2027	10	g [redacted]	g [redacted]	d [redacted]	d [redacted]
2028	0				

Notes
A 1-10% (j [redacted]) annual increase in liquid waste volume, driven by increased demand is assumed.
Cost values are discounted to 2021 year-end price, using a 4% discount factor.

Environmental Considerations:

CO_2 emissions from incineration of downstream user waste containing 4-tert-OPnEO is significant and would partially offset the potential environmental benefit of prevented releases of 4-tert-OPnEO. The waste is a very dilute solution, consisting almost entirely of water. The quantities of waste that would be incinerated annually are conservatively estimated to be 10 – 100 (g) million litres. It is possible to calculate the CO_2 emissions from the incineration given the following reasoning:

The water in the liquid waste must be vaporized before the 4-tert-OPnEO can be burned in the incinerator, which requires energy. There is energy needed to heat the water from 15 to 100°C. Since the energy required to raise the temperature of one gram of water 1°C (the calorie) is 4.1855 joules (Britannia, 2021), the energy required to heat g m3 (tonnes) by 85 degrees is g x 85 x 4.1855 = i GJ. Secondly, there is energy required for the vaporization, known, as the heat of vaporization, which is a physical property of a substance. It is defined as the heat required to change one mole of liquid at its boiling point under standard atmospheric pressure, expressed as kg/mol or kJ/kg. When a material in liquid state is given energy, it changes its phase from liquid to vapor (the energy absorbed in this process, the heat of vaporization). The heat of vaporization of water is about 2,260 kJ/kg (Datt P, 2011). The energy required to vaporize the wastewater can be calculated as g x 2,260 = i GJ.

The total energy to incinerate the wastewater is therefore i GJ + i GJ = i GJ. Assuming that the required energy would be generated using natural gas, the most efficient of the fossil fuels, the carbon dioxide released by burning enough natural gas to produce i GJ can be calculated from the specific carbon dioxide emission factor for natural gas, 56.1 kg CO2/GJ (Volker Quaschning, 2021). The carbon dioxide released from the incineration of the g m^3 (tonnes) of wastewater would therefore be 1,000 – 10,000 (g) tonnes (i x 56.1). This is for this Applicant only. Adding other IVD manufacturers with high throughput analysers would significantly increase the overall burden at a time when GB is working to reduce greenhouse gas emissions.

Conclusion on liquid waste collection by downstream users:

Given the unique considerations for high throughput, fully automated analyser systems, the Applicant requests that a GB Authorization is granted to downstream users for Use 1, without a condition to segregate the waste streams. It should be considered instead to commit the Applicant to the elimination of the emissions within 5.5 years, as documented in the Substitution Plan.

Organisational RMMs: The Applicant has ensured that the system operation manuals provide recommendations for waste handling, stating that each facility is responsible for labelling all waste containers and characterizing its waste stream to ensure waste is disposed of in accordance with the appropriate local, state, and national regulations.

It can be concluded that the Applicant has taken appropriate measures to minimise emissions of 4-tert-OPnEO to the environment to the degree that is technically and practically possible.

10. RISK CHARACTERISATION RELATED TO COMBINED EXPOSURE

10.1 Human health (related to combined exposure)

10.1.1 Workers

No risk characterisation has been conducted for workers as it is not considered relevant for this substance.

10.1.2 Consumers

No risk characterisation has been conducted for consumers as it is not considered relevant for this substance as there is no consumer use.

10.2 Environment (combined for all emission sources)

10.2.1 All uses (regional scale)

10.2.1.1 Total releases

Table 10.2.1 shows the quantities of 4-tert-OPnEO used by downstream users in GB, along with the releases from each use.

- Used reagents from Use 1 – ES1 at the customer sites are released to wastewater for IA and CC tests and as solid waste for ABBOTT PRISM tests.

Table 10.2.1 Total releases to the environment compartments per year per life cycle stages in 2021

Use / ES Number	GB usage (kg 4-tert-OPnEO)	GB releases to wastewater (kg 4-tert-OPnEO)	GB releases to solid waste/landfill (kg 4-tert-OPnEO)	GB waste collected and incinerated (kg 4-tert-OPnEO)
1	10 – 100 ([redacted])	93	0	10 – 100 ([redacted])

Releases to wastewater were assumed to be directed to an STP in their entirety. It is assumed that 4-tert-OPnEO degrades to 4-tert-OP completely and it is discharged to the environmental compartments as predicted by the Chesar for the STP (see Table 9.0.4). Conversion of quantities of 4-tert-OPnEO to 4-tert-OP used a factor of 0.33, which applies for a 4-tert-OPnEO with an average of 9.5 ethoxylation units.

Remarks:

Total releases of 4-tert-OPnEO in GB in 2021 are estimated to be 93 kg. Almost all releases are expected to be released to wastewater and then treated at a local STP. It is assumed that all 4-tert-OPnEO degrades to 4-tert-OP, so a factor of 0.33 was used to convert 4-tert-OPnEO quantities to the degradation product. The share of 4-tert-OP in each environmental compartment after the STP (freshwater, air and agricultural soil) was calculated by the SimpleTreat model embedded Chesar 3.4., as shown in Table 9.0.4.

10.2.1.2 Regional exposure

Environment

No measured regional concentrations are available, as the Applicant is not the only user of 4-tert-OPnEO in GB. So, any measurements would not provide meaningful information for the contribution of the uses applied for to the total concentrations. The regional quantities were derived from a starting point of 10% of total emissions of 4-tert-OPnEO in 2021. So, the total regional releases of 4-tert-OPnEO are approximately 9.3 kg/year and the total regional emissions of 4-tert-OP were approximately 3.1 kg/year. Of these, 10% (0.31 kg/year) are released directly to water, as a

conservative assumption regarding STP coverage of the Applicant's customers. The remaining 2.79 kg 4-tert-OP/year are treated in a STP and are released to water (43%), air (4.8%) and sludge (52.2%).

Table 10.2.2 Predicted regional exposure concentrations of 4-tert-OP (Regional PEC) and risks for the environment based on a wide dispersive use

Protection target	Regional PEC
Fresh water	**Regional PEC:** 1.05E-8 mg/L
Sediment (freshwater)	**Regional PEC:** 1.96E-5mg/kg dw
Marine water	**Regional PEC:** 1E-9 mg/L
Sediment (marine water)	**Regional PEC:** 1.7E-6 mg/kg dw
Air	**Regional PEC:** 3.74E-10 mg/m³
Agricultural soil	**Regional PEC:** 1.97E-8 mg/kg dw

Remarks on measured regional concentrations:

The regional concentrations of 4-tert-OP were calculated using the Chesar 3.4 tool. The default physicochemical and environmental fate properties of the model were used. The only custom input were the releases of the substance to the different environmental compartments, assuming the default 10% regional use share. This factor is based on the widespread use of the IVD kits by the Applicant's customers in GB. A typical region for the purposes of regional risk assessment is assumed to have 20 million inhabitants and an area of 40,000 km^2, i.e. a 200 km square. The Applicant's customer site locations are scattered across GB and it is not likely that there will be such a region containing 10% of the total usage based on current use data. Nevertheless, the 10% regional tonnage share will be used as a conservative approach.

Remarks on risk characterisation for regional concentrations:

The regional environmental concentrations in water in Table 10.2.2 present a rather conservative regional concentration, as it largely assumes that 4-tert-OPnEO is being treated in standard STPs, which achieve a lower dilution than what has been observed during the environmental exposure assessment for individual example local areas in ES1.

Furthermore, the Applicant's customers are hospitals, medical laboratories and clinics or research centres, therefore it was assumed that, as a conservative approach, 90% of the emitted quantities of 4-tert-OPnEO will be treated in an STP. From there, they will be distributed to the environmental compartments according to the release percentages for the model STP, which were calculated by the modelling tool, Chesar. The 10% that will not be treated by an STP is assumed that will be released directly to water.

Man via environment

The scope of this assessment focuses on the environmental exposure only and type of risk characterisation required for human health exposures is not evaluated in this application as the substance has been placed in Annex XIV to EU Regulation 1907/2006 (REACH) on the basis of its endocrine disrupting properties in environmental species and thus its effects and impacts on the environment are only of relevance.

Discussion

Overall, it is considered that the Applicant has taken whatever measures were technically and practically possible to minimise emissions of 4-tert-OPnEO.

In summary:

- Based on hierarchy of control principles, substitution of 4-tert-OPnEO is considered the primary risk management measure. The Applicant prioritised substitution of the product that accounted for 90% of the total 4-tert-OPnEO releases. This product (Trigger) launched in GB in 2020 and is therefore not included in the exposure assessment.
- Collection and incineration is the only treatment method available to eliminate 4-tert-OPnEO releases from the instrument effluent.
- Wastewater volumes are very high. Over 10 – 100 ([redacted]) million liters would have to be collected and incinerated annually in GB. For context, an equivalent assessment of EU volumes determined the quantities to be equivalent to a 2.4% increase in the overall European Union hazardous waste incineration stream (Eurits, 2021).
- Hospital and clinical laboratories do not have existing infrastructure or space to establish new infrastructure capable of handling this volume of wastewater.
- Even if they had the space, the disruption during facility modifications would be unacceptable. These laboratories operate 24/7 and provide critical information to support the provision of healthcare services across GB.
- In the timeframe it would take to complete facility modifications (re-routing of drainage networks and installation of large-scale external holding tanks), the Applicant will have completed most of the product reformulations to remove 4-tert-OPnEO.

Therefore, it can be concluded that sufficient efforts have been undertaken in order to minimise emissions of 4-tert-OPnEO from the use applied for to the degree that is technically and practically possible.

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Appendix I: Uncertainty analysis

A summary review of the uncertainties of the analysis are included at the end of this section as Appendix Table 2.

Sensitivity analysis discussion

The main uncertainty in the CSR would be the fate of 4-tert-OPnEO in the STP and the distribution of the 4-tert-OP, as it is assumed that all 4-tert-OPnEO degrades to 4-tert-OP and there is no removal. Furthermore, it is assumed that the distribution of 4-tert-OP at the waste streams exiting the STP (effluent, air, sludge) will be based on the 4-tert-OP properties. This approach tends to overestimate the emissions through sludge. There is a marked difference if the 4-tert-OPnEO properties are used to determine the distribution, with the majority expected to be in the liquid phase. This could affect the PECs for water and sediment, so it was decided to examine the PECs for the Applicant's sites and some of the customer sites with the highest PECs.

The water PECs would be higher when the 4-tert-OPnEO properties are used. However, the PECs still remain low in all cases. It should also be noted that, as discussed in Appendix Table 2 below the background concentration is most likely overestimated, due to the use of standard STPs for the widespread use exposure assessment, which has a lower dilution factor compared to the actual STPs in the examined customer site locations.

Uncertainty conclusion

The Applicant has attempted to take a worst-case approach whenever possible with the aim of presenting an overall conservative result. It is considered that there is still uncertainty in the analysis, but it does not affect the conclusion in the use applied for, the Applicant has reduced emissions to the degree that is technically and practically possible. Emissions could potentially be reduced further in the downstream users' sites, but that would require disproportionately high capital and operational cost for projects that would become obsolete very soon after the Sunset Date. Furthermore, as mentioned elsewhere in the CSR, the Applicant is committed to prioritising the substitution of 4-tert-OPnEO from the reagents. The current CSR is based on the 2021 values for which there is a substitution program in place. It should be noted that there is little uncertainty with regards to the emitted quantities and most of the uncertainties affect the predicted environmental concentrations provided.

Appendix Table 1: Uncertainty Analysis Review

Uncertainty	Impact for the CSR	Assumption
Fate of 4-tert-OPnEO in the Sewage Treatment Plants. The substance is treated in a multitude of STPs across GB, with different characteristics and processing methods.	Releases of 4-tert-OPnEO and 4-tert-OP from the STPs would differ from location to location. It is also possible that in some STPs, degradation of 4-tert-OP would also be observed, reducing the total emissions.	A conservative approach was followed, by assuming that all 4-tert-OPnEO will degrade to 4-tert-OP in the STPs, without any removal. Distribution to the different compartments of outflow of the STP (water, air, sludge) was determined on the basis of the 4-tert-OP properties, instead of 4-tert-OPnEO. This approach has a greater share of the substance in sludge and agricultural soil. It was used as it was assumed that all emissions would be in 4-tert-OP.
Quantity of 4-tert-OPnEO in reagents per test is not the same across the different assays but varies.	The analysis of releases of 4-tert-OPnEO from the Applicant's downstream users' sites would not be accurate and could over- or underestimate specific local concentrations.	The total usage of 4-tert-OPnEO was aggregated and split evenly across all tests to determine an average quantity of 4-tert-OPnEO in reagents per test. Due to the very large number of tests carried out, this assumption is expected to have little impact to the final results.
Regional concentrations were calculated by Chesar from wide dispersive use using standard STP, which, as determined by the downstream user analysis by the Applicant, was not representative of the STPs in locations of the Applicant's customers.	The calculation seems to overestimate the background concentration levels, giving a higher PEC for the individual local areas.	It was decided to keep the Chesar calculations as a conservative approach. The results from the local area calculations also show low environmental concentrations.
There is uncertainty on the treated volume of wastewater and the flow rates in the rivers at some of the local areas examined in the exposure assessment of the downstream user use.	Predicted Environmental Concentrations may not be accurate, which could lead to over- or underestimations.	The methodology for selection of the Sewage Treatment Plants and the values used in the analysis is described. Conservative assumptions were made where possible. The approach described in the R.16 Guidance document was followed when determining river flow rates. It is thus expected that uncertainty has been minimised.

Appendix II: GB Local Areas, Examples of Specific Data

Local Area No	Emission category*	Receiving STP p.eq**	Receiving water body	Receiving water flow rate† (m3/day)	Total Sum of Reagents Daily		Total sum of Reagents Annually	
					OPnEO (kg/day)	OP (kg/day)	OPnEO (kg/yr)	OP (kg/yr)
1	Very High	574,000	River	4,147,200	[redacted]			
2	High	216,000	River	2,357,683				
3	Medium	198,000	Coastal	Coastal default of 100 used				
4	Low	209,000	River	302,400				

[a]

* Emission ranges. Very high emission range <0.00400; high emission range > 0.00100 to ≤ 0.00400; Medium emission range > 0.00010 to ≤ 0.00100 & Low emission range ≤ 0.00010. All values are in kg/day sum of total reagents OP.

**data was obtained from the EU Urban Waste Water Treatment Map reported by Member States in 2018. Available online at: https://www.eea.europa.eu/themes/water/european-waters/water-use-and-environmental-pressures/uwwtd/interactive-maps/urban-waste-water-treatment-maps. If information was not available, R16 guidance (Section A.16-3.3, Equation R.16-18) was applied.

†River flow figures were taken from the Swedish Meteorological and Hydrological Institute website for EU river flows. Available online at: http://www.water-switch-on.eu/, or literature reference if available. R16 Guidance for average river flow calculations: A.16-3.3.3 Calculation of PEClocal for the aquatic compartment (freshwater). Available online: https://echa.europa.eu/documents/10162/13632/information_requirements_r16_en.pdf. All volumes in m3/day. Figures are averages & divided by 3 as per r16 guidance).