CHEMICAL SAFETY REPORT

Part A and Part B

Sections 9 + 10

Public version

Substance:	Annex XIV entry #42: 4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylate, covering well-defined substances and UVCB substances, polymers and homologues (Triton™ X-100)
Applicant:	Siemens Healthcare Diagnostics Products Ltd
Site:	Llanberis, UK
Use title:	Use of OPE as detergent in the production of bead components for in-vitro diagnostic kits for an immunoassay platform
Use number:	use #1

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Part A

1. SUMMARY OF RISK MANAGEMENT MEASURES

The risk management measures for the Use of OPE as detergent in the production of bead components for in-vitro diagnostic kits for an immunoassay platform are summarised in the document “succinct summary of RMMs and OCs”.

2. DECLARATION THAT RISK MANAGEMENT MEASURES ARE IMPLEMENTED

The risk management measures for workers and the environment as described in the “succinct summary of RMMs and OCs” are implemented at Siemens Healthcare Diagnostics Product Ltd.

3. DECLARATION THAT RISK MANAGEMENT MEASURES ARE COMMUNICATED

Not applicable, since no products containing OPE are supplied to customers

Part B

9 Introduction

9.1 Substance description

Substance subject to authorisation (REACH Annex XIV, entry #42):

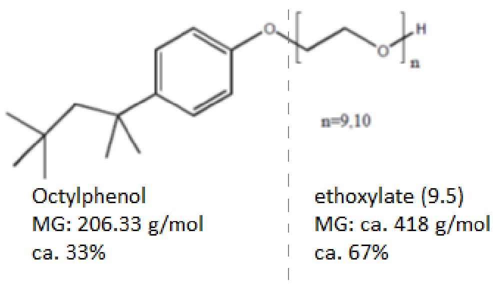
4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated, covering well-defined substances and UVCB substances, polymers and homologues.

Commercial products used in IVD-kits by Siemens Healthcare Diagnostic Products Ltd.

#	Common trade name	Chemical name	Degree of ethoxylation (EO units)
1	Triton™ X-100	(4-(1,1,3,3-Tetramethylbutyl)phenylpolyethylene glycol	9.5 (9 or 10) **$OP_{9.5}EO$**

MG: ca. 625 g/mol

Molecular structure:



9.2 Description of use

Siemens Healthcare Diagnostics Products Ltd uses OPnEO (Triton™ X-100) exclusively at one site located in Llanberis, North Wales, UK as a surfactant in buffer formulations used in the manufacture of in-vitro diagnostic (IVD) products. It is used for the production of key components, specifically antibody or antigen-coated claim #B beads, for the claim #B in-vitro diagnostic platform of automated claim # B immunoassays. It is essential to note that although Triton™ X-100 is a critical raw material required for the successful manufacture of #A analyte bead components (spanning #A claim #B IVD products), it is not present in the final bead components produced.

Remark: The abbreviations OPE and OPnEO are used synonymously in this CSR.

9.2.1 Description of steps related to the use of OPnEO

The manufacture of claim #B IVD analyte beads in Llanberis is undertaken in batch mode and through three consecutive steps, as shown in Figure 1 (ECS 1, ERC 4):

1) **Buffer formulation**: buffer solutions are prepared for use in either bead washing or bead coating. All buffer solutions containing Triton™ X-100 that are required for bead washing and coating are prepared at this step.

   - The OPnEO is weighted and transferred manually to a vessel (WCS 1, PROC 8a) and
   - mixed with water and other buffer ingredients (WCS 1, PROC 5).

   Depending on the buffer, the volume per lot varies between #A l and #A l. In all cases, Triton™ X-100 is present in the buffer solution at concentrations of no more than #A%.

2) **Bead washing and coating**: this takes place in a closed system referred to as the 'Bead Coating Chamber' (see Figure 2) where beads are washed and coated in the pre-prepared buffer solutions prepared in Step 1 (WCS 2, PROC 3).

- *Washing of beads*: OPnEO is used for bead washing during the manufacture of [redacted]IVD analyte beads. The surfactant action of OPnEO is exploited to remove impurities from the bead surface, predominantly [redacted], in preparation for subsequent bead manufacturing steps where analyte-specific antibodies or antigens bind to the clean bead surfaces.

  Out of these [redacted] analyte beads, [redacted] are first prepared by producing a [redacted] bead known as a '[redacted] Bead'. The [redacted] Beads are beads which have been washed in a [redacted] % Triton™ X-100 buffer solution. Once the [redacted] Bead has been prepared, at a next step in the process it is turned into a specific analyte bead via the bead coating of critical raw materials specific to the products (e.g. binding of the [redacted]).

  The remaining analyte bead that uses Triton™ X-100 during bead washing steps is that manufactured for the [redacted] products (IVD analyte bead #[redacted]). This manufacture of this analyte bead effectively has the [redacted] Bead wash step as part of its production process albeit at a reduced concentration of [redacted] %, with subsequent coating steps being free of OPnEO use. In essence, the [redacted] analyte bead has the same production process as the aforementioned [redacted] analyte beads, the only difference being is that [redacted] Beads are prepared and coated in a single process, rather than in two distinct steps.

- *Coating of beads:* the coating cycle acts to bind critical raw materials onto bead surfaces. In the context of [redacted] beads, a critical raw material is defined as a chemical or biomolecule which forms a part of the analyte-capture system of the immunoassay (i.e. the process of binding the analyte of interest found in the patient sample to the bead surface in order to facilitate detection) and as such one which will be present in the final product. OPnEOs are not present in the final product produced; however, for the [redacted] and [redacted] IVD products (IVD analyte beads [redacted] and [redacted]), OPE is used to facilitate the coating of a critical raw material onto the bead, but is not present in the final products..

  For the [redacted] products (IVD analyte bead #[redacted]), the critical raw material in question is [redacted]. The [redacted] is responsible for capturing [redacted] in patient samples onto the bead so that the dose of [redacted] can be measured by the [redacted] analyser. In order to coat the [redacted] onto the bead, three coating solutions containing [redacted]% OPnEO are prepared in Step 1. The surfactant action of Triton™ X-100 is again exploited to stabilise the [redacted] in the buffer medium, in order to minimise or reduce natural aggregation and disintegration processes.

  For the [redacted] products (IVD analyte bead #[redacted]), the critical raw material in question is [redacted]. The mechanism by which the [redacted] immunoassay operates relies upon the presence of this material on the bead to quantify the amount of [redacted] in serum or heparinised plasma samples. In order to coat the [redacted] onto the bead, a coating solution containing [redacted]% OPE is prepared in Step 1. The function of the OPE in this situation is analogous to that described for the [redacted] products, that is to stabilise the critical raw material in an aqueous environment.

3) **Bead drying**: to complete the process the beads undergo drying to produce dry analyte-specific beads which are inserted into the final IVD Kit. OPnEO is not present during this step and the dry beads produced are also OPnEO-free. It is important to emphasise that although OPnEO is absent in the final product, the use of OPE during production of the beads is nevertheless critical

to the performance of the immunoassays and forms part of the product design for all of the impacted [redacted] IVD products.

Figure 1: Schematic description of the use of Triton™ X-100 at Siemens Healthcare Diagnostics Products Ltd for the coating of IVD analyte beads

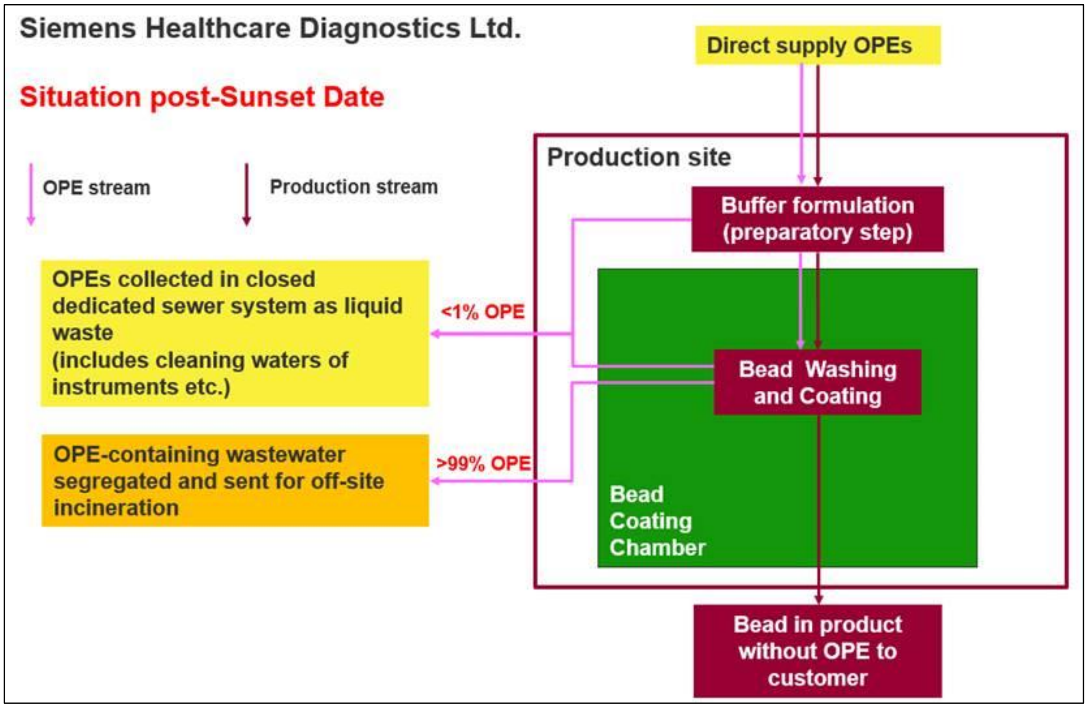


Figure 2: Bead coating chamber where bead washing and coating steps take place

[redacted]

All buffer solutions for washing and coating steps described above are prepared during the buffer formulation step (WCS 1) and this step is identical with regards to Operational Conditions (OC) and Risk Management Measures (RMM) for all types of beads produced by Siemens Llanberis.

All steps are performed by trained personnel and in accordance with ISO 13485 and Good Manufacturing Practices (GMP) which are part of the regulatory requirements for the design and manufacture of medical devices according to FDA 21 CFR Part 820 regulation.

For the washing procedure, Triton™ X-100 is dissolved in water to the required concentration of [redacted]% for IVD analyte beads #[redacted] to #[redacted] and [redacted]% for IVD analyte bead #[redacted]. For the [redacted] coating procedure (IVD analyte bead #[redacted]), three aqueous buffer solutions containing OPE at a concentration of [redacted]% are prepared and for the [redacted] coating procedure (IVD analyte bead #[redacted]), a solution containing [redacted]% OPE is prepared. The washing and the bead coating steps are subject to the same OCs and RMMs. See picture of installation below (Figure 3).

Figure 3: Beads manufacture buffer formulation laboratory

[redacted]

9.2.2 Wastewater treatment

All steps are performed in dedicated areas of the site that are connected to a separate wastewater collection system (see Figure 4), collecting all waste liquids in a tank (Figure 1: WCS 3: PROC 8a, PROC 4), which is then transported by road as waste to an industrial wastewater treatment plant in Liverpool.

Figure 4: Wastewater Collection System

Currently also the wastewater from Bead Manufacture area is gravity-fed by pipe to an 8000L sump (passing through filter box to capture any polystyrene beads) seen in picture. Following this, the wastewater is pumped into the adjacent 4-Tank containment system with a capacity of 90,000L. This is emptied 2-3 times a week, where it is vacuum pumped into a tanker barrel of ca. 25 m³ and transported ~100 miles by road to an industrial wastewater treatment plant (#B [redacted]). In this plant the wastewater is treated with lime for precipitation and removal of phosphates. After precipitation the aqueous phase is separated and fed into the Liverpool municipal sewage treatment plant (WwTW).

A new risk management measure will be implemented before the sunset date in order to reduce environmental OPE releases from bead coating and washing by more than 99% (see AoA Appendix 3). This measure foresees the segregation of OPE-containing buffers from the bead coating chamber and sending this for off-site incineration. To ensure this, certain V-mixers would need to be restricted so OPE-containing buffers were used on this production equipment only. Internal tank system would need to be installed for draining of those V-Mixers and also pipework to feed an external collection point (see Figure 1, WCS 5: PROC 8a, PROC 3). The volume of wastewater separated for incineration as hazardous waste would be ca. 150 t/year (ca. 12 t/month) in 2021. It is assumed that OPE is completely degraded during incineration (see separate CSR section 4.4).

The remaining OPE (< 1%) resulting from cleaning of equipment and installations (WCS 1 and 2) will still be discharged together with the other wastewater (WCS 3) to be treated in Liverpool and this way enter the STP and finally the environment.

A small proportion of the applied OPnEO (assumption: < 0.1%) adheres to solid waste like pipettes, gloves, wipes, which are collected as solid laboratory waste (WCS 4, PROC 21) for incineration. Since this volume cannot be adequately quantified, it was not considered in the calculation of emissions to wastewater.

9.3 Introduction to the assessment for the environment

9.3.1 Use of OPE as detergent in the production of bead components for in-vitro diagnostic kits for an immunoassay platform

Table 1: Tonnage for assessment (estimation for 2021)

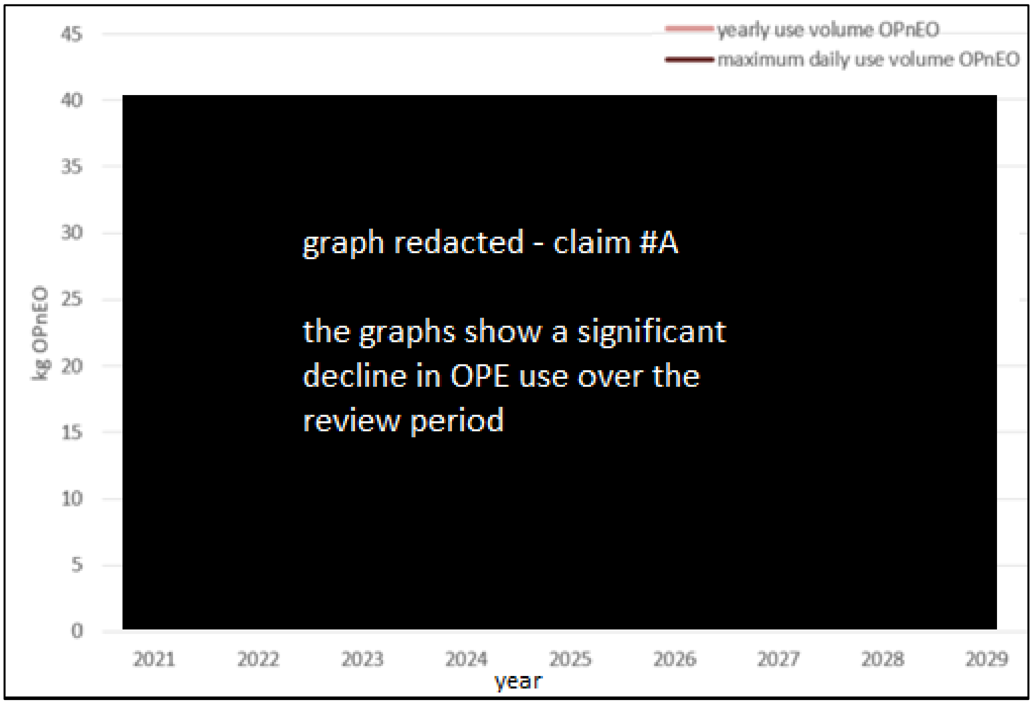
ES#	**Exposure scenario (ES) name and related environmental contributing scenarios**	**Tonnage per use (t/year)**	**maximum tonnage per week**	**Daily local tonnage (t/day)**	**Annual local tonnage (t/year)**
ES1 (IS)	OPE as detergent in the production of bead components for in-vitro diagnostic kits for an immunoassay platform considering [redacted] kg OPE/year used for buffer production at Llanberis [redacted] kg OPE/year contained in [redacted] solution from Siemens Marburg	[redacted]			
	- OPE as detergent in the production of bead components for in-vitro diagnostic kits for an immunoassay platform (ERC 4)		[redacted]	[redacted]	[redacted]

In line with [redacted] leading to the complete phase out of OPE. [redacted] (see Table 11 and Figure 11 in annex 11.2).

Accordingly, the yearly local release of OP due to bead manufacture at Llanberis will decrease [redacted]. The local exposure estimation in the exposure scenarios (section 9.4) is based on the maximum daily local tonnage. The maximum daily release of [redacted] kg OPnEO (daily local tonnage, Table 1) is estimated based on the maximum number of lots prepared during one week, considering the collection of wastewater and discharge of it happens 2 times per week (lower value used as a worst case, see section 0). In the first instance the maximum daily tonnage will not change, even if the yearly volume decreases, while the frequency of weeks with this maximum lots and tonnage will decrease. However, after the implementation of the additional risk management measure the daily release will be reduced by more than 99% to [redacted] g/day in 2021 (see 9.2.2).

Assuming a regular capacity utilization of the facilities for bead bead manufacture, it can be expected that the probability of events with the assumed maximum release will decrease, while the probability of a lower daily tonnage due to a lower number of lots produced during one week will increases. Actual figures are difficult to predict, but for a first approximation it is assumed that with the yearly decrease of the local tonnage also the daily local tonnage will decrease, but only subsequently (Figure 5):

Figure 5: Estimated decrease of yearly and maximum daily use volume of OPnEO



9.3.2 Summary of risk management measures and operational conditions to reduce environmental releases

OPnEO is handled exclusively by well trained personnel in areas with restricted access. All OPnEO containing wastewaters are collected, transported to the Liverpool WwTW and pre-treated before release to the treatment plant. This way unintended releases to the local environment at Llanberis site can be excluded. Currently (2019), nearly all OPnEO used at Llanberis ends up in the wastewater treatment and the degradation product OP after deduction of OP bound to sludge enters the environment of the wastewater treatment plant in Liverpool.

However, with the planned implementation of the segregation of the OPnEO-containing buffers after use in the V-mixers the major fraction of OPnEO containing wastewater will be sent for incineration as hazardous waste and complete degradation of OP. Thus, the emission of OPnEO and finally OP to the environment after sunset date will be reduced by more than 99%, less the 1% of the OPnEO used at Llanberis will enter the normal wastewater stream and the environment.

Since the concentration of OPnEO in the solutions after use is low, further separation and treatment of the wastewater is considered unsuitable to reduce the remaining OP-emissions to the environment (see also separate AoA-document). The most effective measure to reduce the OPnEO-release and thus the OP environmental concentration is the claim #B, #C (see 9.3.1).

The environmental burden for the River Mersey and the Irish Sea as well as the regional concentrations will be reduced with the reduced OPnEO releases from bead manufacture claim #C

9.3.3 Description of the receiving water (River Mersey and Irish Sea)

The aqueous waste (ca. 25 m³ at 3 days per week) is transported to an industrial wastewater treatment plant at Liverpool, where it is treated with lime for precipitation and removal of phosphate. After precipitation the aqueous phase is separated and fed into the Liverpool municipal sewage treatment plant (WwTW).

The Liverpool Wastewater Treatment Works (WwTW) are located at Sandon Dock in the Port of Liverpool about 5 km distance from the Mersey estuary to the Irish Sea. The estuary has one of the largest tidal ranges in Britain. The mean spring tide is up to 9m.

A typical freshwater flow from the river is 66m^3/s whilst the tidal influx into the Narrows is 2000m^3/s during a spring tide (Ref. 8). Freshwater flows vary seasonally from 25 - 200 m^3/s (Ref. 9), with flood flows exceeding 1200 m^3/s (Ref. 10).

For the modelling a constant fluvial input of 36m^3/s was used, which calculates to a daily flow rate of 3,100,000 m^3/day (Ref. X).

Wastewater flow to Liverpool WwTW: 365,000 m^3/d[1]

The sludge in the Liverpool WwTW is further dewatered before gently heating the sludge in anaerobic digesters to gain biogas[2]. The treated sludge is temporarily stored before being transported/pumped to the Mersey Valley Processing Centre for incineration[3]. It is assumed that the OP in the sludge is completely destroyed during incineration.

9.3.4 Assumed fate and behaviour of OPnEO during use and wastewater treatment

The RAC Q&A-paper[4] related to the application for authorisation OPnEO and NPnEO answers the questions on which substances and/or degradation products should be addressed in the chemical safety assessment in application for authorisation for OPnEO and NPnEO (question 1), that the assessment should focus solely on the degradation product OP and the identified endocrine disrupting properties. In its application Siemens Healthcare Diagnostics Products Ltd follows the approach to consider the degradation of OPnEO in the aquatic compartment after anaerobic wastewater treatment, taking into account, that the average proportion of OP in the applied OPnEO commercial product is 1/3 (see also section 4.5 of the CSR in a separate document).

Ethoxylated alkylphenols are enzymatically degraded in wastewater by shortening the polyethoxylate chains and hydrophobic alkyls. With the decreasing chain length, the water solubility of the molecule decreases while its tendency to adsorb to sludge and organic matter increases.

According to the European Risk assessment report on Nonylphenolethoxylates (NPnEO) reasonable worst-case assumptions for the fate of NPnEO during anaerobic wastewater treatment, it may be predicted that the major amount of undegraded NPnEO is directed to the effluent (25 %), and the sewage sludge represents the secondary sink, receiving 19.5 % of the initial amount of NPnEO. It is assumed that OPnEO behaves in the same way.

Based on the assumption above OPnEO is partly degraded and 19.5 % is adsorbed to sludge while the remaining OPnEO and degradation products are discharged with the WwTW effluent. However, since only the OP-part of the molecule is relevant for the environmental risk assessment, the different degradation products are not further considered in the model and it is assumed that all OPnEO released to the environment is finally degraded to OP, which represents on average 33% of the molar mass of OPnEO depending on the ethoxylate chain length.

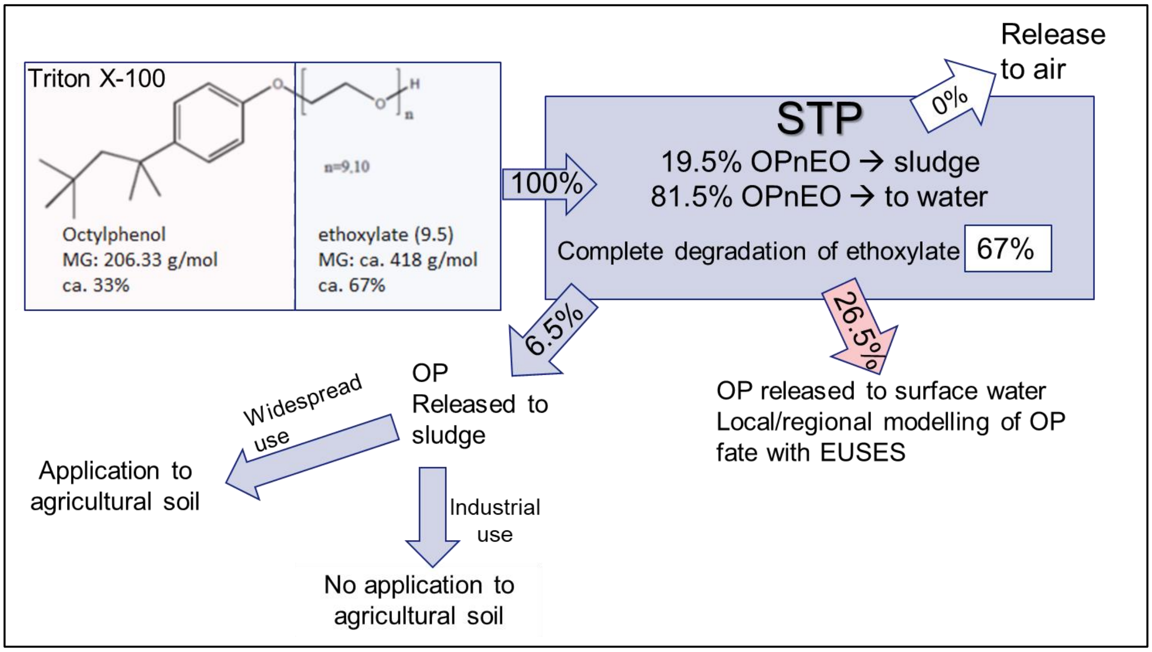
[1] http://www.waterprojectsonline.com/case_studies/2015/UU_Liverpool_2015.pdf

[2] Notice of variation and consolidation with introductory note, The Environmental Permitting (England & Wales) Regulations 2016

[3] https://www.edie.net/library/Giant-sludge-incineration-plant-opens-in-the-Mersey-Valley/1745

[4] Committee for risk assessment, 2017: Risk related considerations in application for authorisation for endocrine disrupting substances for the environment, especially OPnEO and NPnEO, Agreed at RAC-43

Figure 6: Assumptions on the degradation and behaviour of Triton X-100 in STP



In the absence of bacteria OPnEO is regarded as stable. Thus, OPnEO will not be degraded during formulation and application of the buffers, nor during collection and transport of wastewater. Even the precipitation with lime should not lead to significant degradation. The concentration of OPnEO in the wastewater treated with lime for phosphate precipitation is calculated to be < [redacted]% OPnEO per liter. It can be assumed that the OPnEO partly adsorbs to the precipitate and is this way removed from the aqueous phase. This assumption is partly confirmed by analysis of the Triton X-100 content in wastewater samples before and after the precipitation. Measurements show the same or a slightly lower concentration after the treatment (Annex 11.1, Table 10). Since the measured values are below the level of detection of OPnEO in water the share of OPnEO removed from the wastewater with the precipitate cannot be quantified. Based on this, the removal of OPnEO from wastewater by phosphate precipitation is considered ≥ 0 and the exposure assessment assumes ≤ 100% of the OPnEO (worst case: [redacted] kg/d) in the wastewater is discharged to the sewage treatment plant. After implementation of the segregation system for OPnEO containing buffers (see 9.2.2) the daily release will be reduced to a maximum of [redacted] g and the concentration in this remaining wastewater will be < 0.0001%.

The WwTW is located in Liverpool and the effluent flows to the River Mersey, which flows to the Irish Sea.

No release to air and soil is assumed, since OPnEO is not volatile and the formation of aerosols during use can be excluded. Direct releases of OPnEO-containing products or wastewaters to the local environment can be excluded.

The following distribution of OP-molecules after STP is considered a reasonable worst case estimation for use of OPnEO at Llanberis (Table 2).

Table 2: Releases of OP after STP for TritonX-100 (estimated use figures for 2021)

fate referring to OP in OPnEO in STP	initial OPnEO	OP	EO	compartment
originally released OPnEO	**100%**	**33%**	**67%**	
release to sludge	19.5%	6.5%	13.0%	sludge/soil
mineralisation of dissolved OPnEO	54.0%	0%	54.0%	
OP not adsorbed to sludge and released to water	26.5%	26.5%	0%	water/sediment
calculated efficiency used for exposure estimation concerning how much OP is released to water from initially discharged OPnEO		73.5%		
maximum local release of OP from bead manufactureto water within one year **before** implementation of additional RMM (2021)	#A kg	#A kg		water/sediment
maximum local release of OP bead manufactureto water within one year **post sunset date** (2021)	#A kg	#A g		water/sediment
maximum local release of OP from bead manufacture to water within one day **before** implementation of additional RMM (2021)	#A kg	#A kg		water/sediment
maximum local release of OP from bead manufacture to water within one day **post sunset date** (2021)	#A g	#A g		water/sediment

*assumptions based on the expected molecular weight

9.3.5 Scope and type of assessment for the environment

The RAC Q&A-paper states, that RAC will not develop reference PNEC values or dose-response relationships for OPnEO. An applicant may choose to assume that OPnEO is a non-threshold substance for the purpose of the AfA (question 5). Based on this and the conclusions in the report by Ramboll Siemens Healthcare Diagnostics Products Ltd assumes that OPnEO is a non-threshold substance for the purpose of this AfA. The risk assessment is thus qualitative.

However, in order to get indicators for the relevance of the predicted environmental concentrations and the assumed decrease during the review period, the available data on effects and existing environmental thresholds have been used to determine so called “latest research values” (see section 7.4 in the separate CSR document and Table 3). These values are not used as no effect levels, but are considered indicative values for potential effects due to predicted environmental concentrations.

As requested by the RAC Q&A paper, the environmental exposure is calculated based on reasonable worst case assumptions for the release of OP from the use of OPnEO (see section 4.5 of the separate CSR document). The calculation was performed with Chesar/EUSES applied to the degradation product OP. The resulting PECs are compared with the latest research values (Table 3) in order to get a better understanding on the relevance of the exposure levels and the intended emission reduction.

Table 3: Summarised latest research values used for environmental risk characterisation[5]:

compartment	latest research value	based on
Freshwater	**0.034 µg/L**	NOEC of 0.34 µg/L Gastropods, number of new embryos/eggs
Saltwater	**0.0034 µg/L**	based on AF 10 freshwater /marine water
Sediment	**0.028 mg/kg (dry weight)**	calculated (EPM)
Marine sediment	**0.0028 mg/kg (dry weight)**	based on AF 10 freshwater /marine water
Soil	**0.0056 mg/kg (dry weight)**	calculated (EPM)

Physicochemical properties used for exposure estimation

The following substance properties are used in the fate estimation done by EUSES. They correspond to the degradation product of OPnEO.

Table 4: Substance key phys-chem and fate properties of OP[6]

Substance property	**Value**
Molecular weight	≥ 206.3
Molecular weight used for the assessment	206.3
Melting point at 101 325 Pa	85 °C
Vapour pressure	2 Pa at 38 °C
Partition coefficient (Log Kow)	4.8 at 22 °C
Water solubility	7 mg/L at 20 °C
Henry's law constant (in Pa m3/mol)	574 at 278 K
Biodegradation in water: screening tests	inherently biodegradable
Half-life in freshwater	51 d
Bioaccumulation: BCF (aquatic species)	740 L/kg ww
Adsorption/Desorption: Koc at 20 °C	2.51E3

9.3.6 Comments on assessment approach for the environment

The regional concentrations are reported in section 10.2.1.1. The local Predicted Exposure Concentrations (PECs) reported for each contributing scenario correspond to the sum of the local concentrations (Clocal) and the regional concentrations (PEC regional).

These values are considered a reasonable worst case, since they focus on the OP-content in the applied OPnEO and are based on daily use volumes that may occur if the maximum number of lots is produced in one week and a high proportion of the used OPnEO enters one wastewater tank, which is further treated at Liverpool WwTW.

9.3.7 Scope and type of assessment for man via environment

The scope of exposure assessment and type of risk characterisation required for man via the environment are not considered in this assessment, since human health hazards are not covered by this assessment.

[5] Source: Ramboll Environment & Health GmbH, Patricia Janz, Christiane Brandt, Derivation of the PNEC or dose-response relationship for endocrine disrupting properties of 4-(1,1,3,3-tetramethylbutyl) phenol, ethoxylated (OPNEO), February 28, 2019

[6] Source: ECHA dissemination https://echa.europa.eu/de/brief-profile/-/briefprofile/100.004.934 (status: September 2018)

9.3.8 Introduction to the assessment for workers

With regard to human health effects OPnEO is classified as harmful if swallowed (H302), skin irritating (H315) and serious eye damage (H318). No DNELs have been derived for the substance.

Siemens Healthcare Diagnostics Products Ltd uses Triton X-100 as a laboratory chemical at laboratory scale for preparation of buffer solutions and bead manufacture. Only laboratory workers with related training apply OPnEO according to related and laboratory procedures and under high laboratory hygienic standard including the use of laboratory personal protection equipment (gloves, goggles, coats and shoes). Workers may use OPnEO-containing solutions up to 8 h per day and 5 days per week.

Under these conditions no health risks for workers related to the use of OPnEO are expected

9.3.9 Introduction to the assessment for consumers

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

9.4 Exposure scenario 1: Use at industrial sites – OPE as detergent in the production of bead components for in-vitro diagnostic kits for an immunoassay platform (bead manufacture)

Product category used: PC 21: Laboratory Chemicals

Sector of use: SU 0: Manufacture of medical and dental instruments and supplies (NACE code C32.5)

Technical Function: surfactant

Environment contributing scenario(s):		
ECS 1	OPE as detergent in the production of bead components for in-vitro diagnostic kits for an immunoassay platform	ERC 4
Worker contributing scenario(s):		
WCS 1	mixing of buffer solution for own use	PROC 5, PROC 8a
WCS 2	bead washing and coating	PROC 3
WCS 3	collection, transport and treatment of waste water	PROC 8a, PROC 4
WCS 4	collection, transport and disposal of solid waste	PROC 21
WCS 5	collection, transport and disposal of liquid waste	PROC 8a, PROC 3

Further description of the use: use of OPnEO containing buffer for coating and washing of beads (see section 9.2.1 for detailed description).

9.4.1 Env CS 1: OPE as detergent in the production of bead components for in-vitro diagnostic kits for an immunoassay platform (ERC 4)

The following assessment considers the collection and treatment of waste water before and after the implementation of a segregation system ("additional RMM") for consumed OPnEO-containing buffer after bead washing (see 9.2.2). The wastewater not disposed of as hazardous waste for incineration is discharged to Liverpool WwTW and local water (river Mersey).

9.4.1.1 Conditions of use

Amount used, frequency and duration of use (or from service life)
• Daily use amount at site: <= #A E-3 tonnes/day (2021) *Max volume of OPnEO that could be used in a week (very worst case) = #A kg* *Assuming distribution of lots over the week the maximum volume of OPnEOs that may enter one of the two wastewater tank tanks per week is assumed #A kg before and #Ag after implementation of additional RMM.*
• Annual use amount at site: <= claim #A tonnes/year (2021)
Conditions and measures related to biological sewage treatment plant
• Biological STP: Effectiveness Water: 73.5% • additional RMM: collection and off-site incineration: Effectiveness Water: >99% post sunset date
• Discharge rate of STP: >= 3.65E5 m3/day (*Liverpool WwTW flow rate)*
• Application of the STP sludge on agricultural soil: No
Conditions and measures related to external treatment of waste (including article waste)

• Particular considerations on the waste treatment operations: No (low risk) *Low risk assumed for waste life stage. Solid waste is incincerated and any adhering OPnEO is completely destroyed. Waste disposal according to national/local legislation is considered sufficient.*
Other conditions affecting environmental exposure
• Receiving surface water flow rate: >= 3.11E6 m3/day *average flow rate of the river Mersey at the place of the Liverpool WwTW*

Fate (release percentage) in the biological sewage treatment plant

The biological STP is site specific and the releases to the various compartments have been set by the assessor They are distributed in the following way:

Release to water	26.5%
Release to air	0%
Release to sludge	6.5%
Release degraded	67%

Explanation: Fate (release percentage) in the biological sewage treatment plant (UK, 2005) and degradation to OP (33%)

9.4.1.2 Releases

The local releases to the environment are reported in the following table. Note that the releases reported do not account for the removal in the modelled biological STP.

Table 5: Local releases to the environment

Release	Release estimation method	Explanations
Water	ERC	**Release factor before on site RMM:** 100% **Release factor after on site RMM:** 100% **Local release rate:** #A kg/day
water	*estimated release factor post sunset date*	***Release factor before on site RMM: 100%*** ***Release factor after on site RMM: < 1%*** ***Local release rate:*** #A *g/day*
Air	Estimated release factor	**Release factor before on site RMM:** 0% **Release factor after on site RMM:** 0% **Local release rate:** 0 kg/day **Explanation:** due to low volatility of OPnEO
Non agricultural soil	Estimated release factor	**Release factor after on site RMM:** 0% no release to soil, all OPnEO is discharged via wastewater

Releases to waste

Release factor to external waste: 0.1 % adhered to solid waste from pipettes, gloves and wipes (see section 9.1.1 for further explanation).

9.4.1.3 Exposure and risks for the environment

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table. The exposure estimates have been obtained with EUSES 2.1.2 unless stated otherwise.

Table 6: Exposure concentrations and risks for the environment before implementation of additional RMM

Protection target	Exposure concentration	latest research values	qualitative risk characterisation
Fresh water	**Local PEC:** #A E-4 mg/L	**0.034 µg/L**	calculated local freshwater concentration of OP is above latest research value (factor 3). Risks for aquatic organisms are possible
Sediment (freshwater)	**Local PEC:** #A mg/kg dw	**0.028 mg/kg dw**	calculated local freshwater sediment concentration of OP is similar to latest research value; risks for sediment organisms cannot be excluded
Marine water	**Local PEC:** #A E-5 mg/L	**0.0034 µg/L**	calculated marine water concentration of OP is above latest research value (factor 3) risks for marine organisms are possible
Sediment (marine water)	**Local PEC:** #A E-3 mg/kg dw	**0.0028 mg/kg dw**	calculated marine sediment concentration of OP is similar to latest research value risks for sediment organisms cannot be excluded
Agricultural soil	**Local PEC:** #A E-9 mg/kg dw	**0.0073 mg/kg dw**	compared to the latest research value the calculated concentration of OP in soil is low. Although risks for soil organisms cannot be entirely excluded they are considered unlikely

Most critical values are marked in red..

Table 7: Exposure concentrations and risks for the environment post sunset date

Protection target	Exposure concentration	latest research values	qualitative risk characterisation
Fresh water	**Local PEC:** #A E-6 mg/L	**0.034 µg/L**	compared to the latest research value the calculated concentration of OP in freshwater is low. Although risks for freshwater organisms cannot be entirely excluded they are considered unlikely.
Sediment (freshwater)	**Local PEC:** #A E-4 mg/kg dw	**0.028 mg/kg dw**	compared to the latest research value the calculated concentration of OP in sediment is low. Although risks for sediment organisms cannot be entirely excluded they are considered unlikely.
Marine water	**Local PEC:** #A E-7 mg/L	**0.0034 µg/L**	compared to the latest research value the calculated concentration of OP in marine water is low. Although risks for marine organisms cannot be entirely excluded they are considered unlikely.

Protection target	Exposure concentration	latest research values	qualitative risk characterisation
Sediment (marine water)	**Local PEC:** [redacted]E-5 mg/kg dw	**0.0028 mg/kg dw**	compared to the latest research value the calculated concentration of OP in marine sediment is low. Although risks for marine sediment organisms cannot be entirely excluded they are considered unlikely.
Agricultural soil	**Local PEC:** [redacted]E-11 mg/kg dw	**0.0073 mg/kg dw**	compared to the latest research value the calculated concentration of OP in soil is low. Although risks for soil organisms cannot be entirely excluded they are considered unlikely

9.4.2 Estimated development of local releases and environmental concentrations

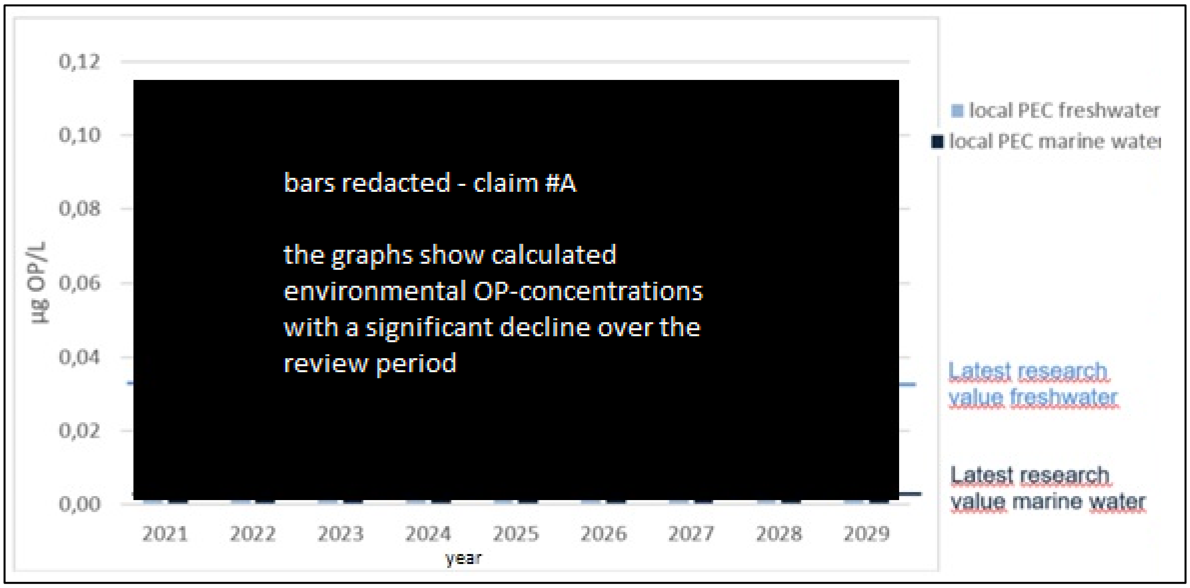
The implementation of the segregation system for OPnEO containing buffers after bead manufacture before the sunset date is considered a very effective risk management measure, since it will reduce the OP emissions to the environment from this use by more than 99%. As risks for the environment can still not be excluded even for low environmental OP-concentrations, the stepwise phase-out of OPnEO-uses at Llanberis is planned.

In line with [redacted], the yearly local release of OP due to bead manufacture at Llanberis will [redacted]. However, the local exposure estimation in the exposure scenarios (section 9.4) is based on the maximum daily local tonnage. The maximum daily release of [redacted] kg OPnEO before and of [redacted] g after implementation of the additional RMM is estimated based on the maximum number of lots prepared during one week, considering the collection of wastewater and discharge of it 2 times per week (see section 0). In the first instance the maximum daily use will not change, even if the yearly volume decreases, while the frequency of weeks with this maximum lots and tonnage will decrease.

Assuming a regular capacity utilization of the facilities for bead manufacture, it can be expected that the probability of events with the assumed maximum release will decrease, while the probability of a lower daily use due to a lower number of lots produced during one week will increase. Actual figures are difficult to predict, but for a first approximation it is assumed that with the yearly decrease of the local tonnage also the daily local tonnage will decrease, but only subsequently:

Based on the assumed decrease of maximum daily tonnages the environmental concentrations will decrease gradually by around [redacted] until 2029 (Figure 7).

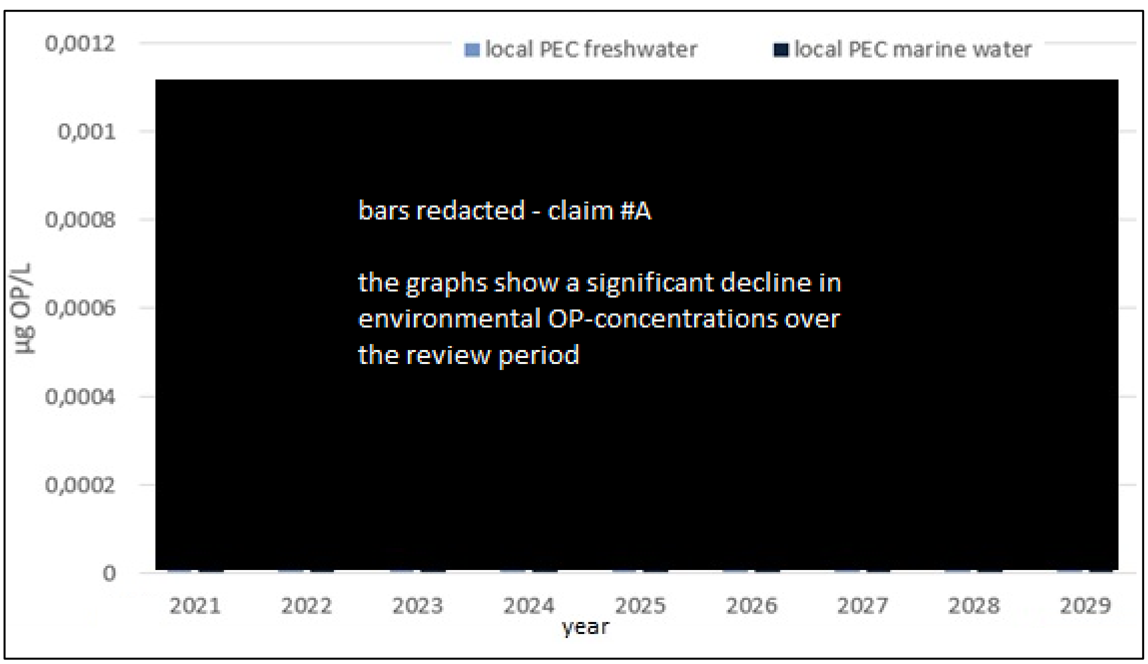
Figure 7: Development of local aquatic PECs of OP related to the use of OPnEO at Llanberis before implementation of additional RMM



The gradual decrease of the use of OPnEO at Llanberis will result in reduced releases to the environment and thus lower environmental concentrations. The comparison with the latest research values for the aquatic compartment shows, however, that the local PECs for freshwater and marine water and for sediments are still above or similar to these indicative values until termination of the use.

Accordingly the local PECs calculated for the situation after implmentation of the segregation system for OpnEO containing buffers are factor 100 lower and thus considerably lower than the latest research values (see Figure 8).

Figure 8: Development of local aquatic PECs of OP related to the use of OPnEO at Llanberis after implementation of additional RMM



The latest research value for soil and sediment lie outside this scale. The PECs for sediment and marine sediment will decrease accordingly.

10 RISK CHARACTERISATION RELATED TO COMBINED EXPOSURE

10.1 Environment (combined for all emission sources)

10.2 All uses (regional scale)

10.2.1.1 Total releases

The total releases to the environment from all the exposure scenarios covered are presented in the table below. This is the sum of the releases to the environment from all exposure scenarios addressed.

Table 8: Total releases to the environment in 2021 from all life cycle stages

Release route	Total releases per year
Water	claim #A kg/year before implementation of RMM
	claim #A kg/year post sunset date
Air	0 kg/year
Soil	0 kg/year

10.2.2 Regional assessment

The regional predicted environmental concentration (PEC regional) and the related risk characterisation ratios are presented in the table below. For the regional scenario only the release figures after implementation of the additional RMM are considered.

The exposure estimates have been obtained with EUSES 2.1.2 unless stated otherwise.

Table 9: Predicted regional exposure concentrations (Regional PEC) and risks for the environment post sunset date

Protection target	Exposure concentration	latest research values	qualitative risk characterisation
Fresh water	**Regional PEC:** #A E-7 µg/L	**0.034 µg/L**	compared to the latest research value the calculated concentration of OP in freshwater in the regional scenario is low. Although risks for freshwater organisms cannot be entirely excluded they are considered unlikely
Sediment (freshwater)	**Regional PEC:** #A E-7 mg/kg dw	**0.034 mg/kg dw**	compared to the latest research value the calculated concentration of OP in freshwater sediment in the regional scenario is low. Although risks for sediment organisms cannot cannot be entirely excluded they are considered unlikely
Marine water	**Regional PEC:** #A E-8 µg/L	**0.0034 µg/L**	compared to the latest research value the calculated concentration of OP in marine water in the regional scenario is low. Although risks for marine organisms cannot be cannot be entirely excluded they are considered unlikely

Protection target	Exposure concentration	latest research values	qualitative risk characterisation
Sediment (marine water)	**Regional PEC:** #A E-8 mg/kg dw	**0.0034 mg/kg dw**	compared to the latest research value the calculated concentration of OP in marine water sediment in the regional scenario is low. Although risks for sediment organisms cannot be cannot be entirely excluded they are considered unlikely
Agricultural soil	**Regional PEC:** #A E-11 mg/kg dw	**0.0073 mg/kg dw**	compared to the latest research value the calculated concentration of OP in soil in the regional scenario is low. Although risks for soil organisms not be entirely excluded they are considered unlikely

10.2.3 Estimated development of regional environmental concentrations

All regional PECs of OP resulting from the use of OPnEO in bead manufacture in Llanberis are two magnitudes of order or more below the latest research values.

In line with claim #C (see AoA), claim #C [redacted]. Accordingly, the yearly releases of OP due to bead manufacture will decrease #C (Figure 9). Subsequently, the regional environmental concentrations will decline in Figure 10.

Figure 9: Projections of use volumes of OPnEO in Llanberis

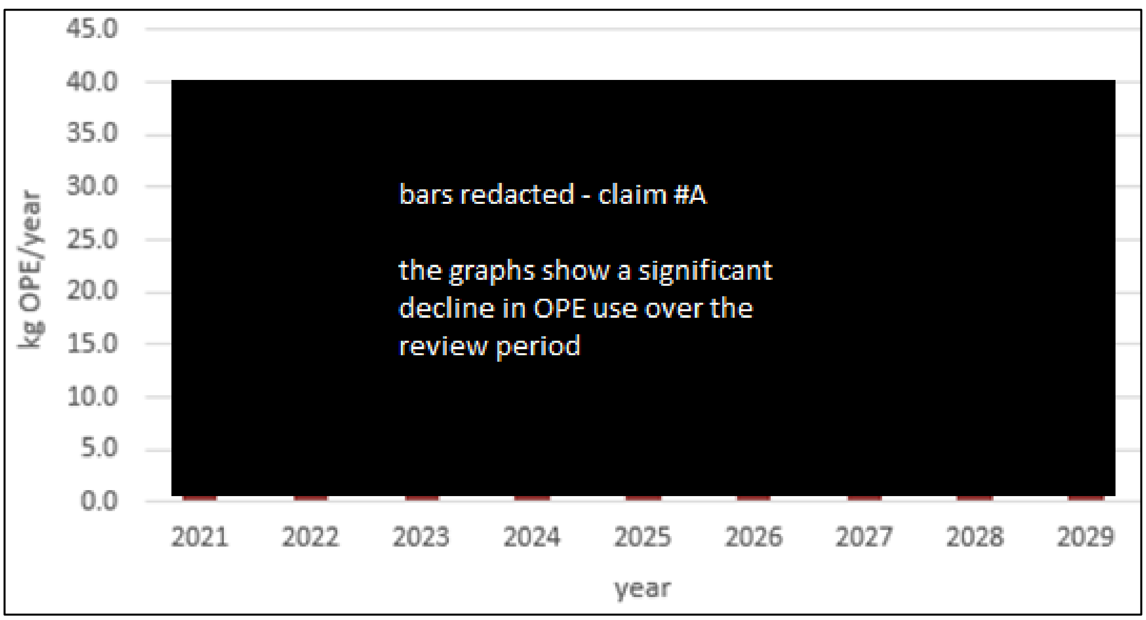
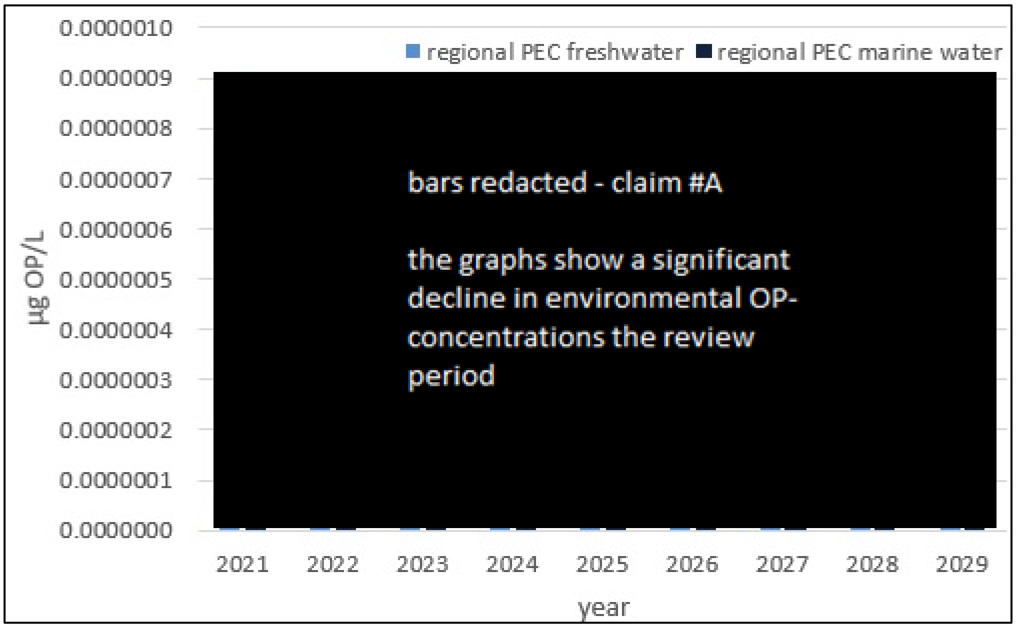


Figure 10: Estimated decrease of regional aquatic PECs of OP due to use of OPnEO in bead manufacture post sunset date



The latest research values lie outside this scale. The PECs for sediment and marine sediment will decrease accordingly.

10.2.4 Local exposure due to all widespread uses

Not relevant as there are no widespread uses covered in this CSR.

10.3 Summary of risk conclusions

Environmental OP-concentration calculated for 2021 for the local scenario based on currently availailable risk management measures (2019) are in the range or above the latest research values for risk characterisation. The implementation of an additional RMM (to be completed in 2020) will reduce the OP-emissions from this use and thus the calculated environmental concentrations by more than 99%.

Further reduction of OP-emissions from bead manufacture will be achieved by stepwise phase-out of OPnEO uses at Llanberis. Even though the use volumes of OPnEO for bead manufacture in Llanberis will decrease [redacted] #C (Table 11) the maximum daily use volumes of OPnEO will not decrease to the same extent (Figure 5), since the size of the related batches will not be reduced, but only the frequency of production lots (11.3.2). Accordingly, in the local scenario the calculation of PECs based on the maximum daily use volumes in the years 2021 to 2029 results in PECs for the aquatic compartment, which decrease much slower than the yearly uses. An additional significant risk reduction for the local environment will be thus achieved [redacted] claim #C in 2030.

Since the sludge from the Liverpool WwTW is not applied to agricultural soil, the related PECs in the local scenario are far below the latest research values.

The estimated release and the calculation of environmental concentrations above are considered reasonable worst case. Based on the following aspects the exposure is considered to be an overestimation rather than an underestimation:

- The calculated maximum use volumes of [redacted] #A kg OPnEO in 2021 and the lower figures for the following years are a worst case assumption. Events, in which the released OPnEO from the batches may end up in one wastewater tank, will not occur very often, if at all. Thus, the regular environmental OP concentrations due to discharge of OPnEO may be factor 2 or 3 lower.

- While the median net flow of the River Mersey was used for the modelling the real dilution by tidal water will be much higher than calculated, as the Mersey river has a tide of about 9m. Since the release of OP from the use of OPnEO in Llanberis occurs maximum 3 times per week and not continuously, it can be assumed that the effective environmental concentration will be lower.
- Microorganism present in the WWTW and in the local industrial environment are probably adapted to OP and thus environmental degradation may happen faster than considered in the calculation.
- It can be assumed that the OPnEO disposed of with the wastewater is partly removed from the wastewater stream with the phosphate precipitate and thus the OP-load of the wastewater forwarded to the WwTW should be lower. The effect can, however, neither be proven nor quantified.
- Liverpool WwTW is a very large and modern STP with high standards. Longer retention times than considered in the calculation can be assumed and will reduce the OP released from STP, while the OP in the sludge will increase. Since the STP sludge from Liverpool is incinerated, the OP bound to sludge will not contribute to environmental pollution.

Overall, although the calculated worst case local and regional PECs are significantly below the latest research values, risks for the local and the regional environment cannot be excluded. According to the review of available data (see section 7 of the separate CSR-document) the most sensitive endpoints describing effects on OP have been observed for gastropods and the number of new embryos/eggs. While the latest research values have been derived based on the related NOEC, this cannot be considered a no effect concentration at all. Other endocrine effects on aquatic and sediment organisms at even lower concentrations cannot be excluded. Thus, even based on the reduced release figures of OPnEO and the resulting reduced environmental OP-concentrations, risks for aquatic and sediment organisms due to the use of OPnEO cannot be excluded until the complete phase-out of the substance.

The implementation of the segregation system for OPnEO-containing buffers and their off-site incineration as hazardous waste in combination with the stepwise phase-out of OPnEO-use as planned by Siemens Healthcare Diagnostic Products Ltd are considered appropriate measures to reduce the environmental risk at local and regional scale effectively. The lack of reliable safe levels for environmental concentrations will question any reduction of emissions without termination. Any activities in this regard will thus focus on short-term minimisation and long-term the complete phase-out of OPnEO uses by Siemens Healthcare Diagnostic Products Ltd.

11 Annex

11.1 OPnEO analysis in wastewater

Wastewater from Llanberis has been analysed before (Siemens Original) and after phosphate precipitation (treated effluent).

Limit of quantitation is currently 0.025% (250ppm) which is below the ppb requirements for wastewater. LOD is 0.01% (100ppm).

Table 10: Results of OPnEO analysis in wastewater streams

[redacted] claim #B

DATA SUMMARY

ISO 9001

Client: Siemens Healthcare Diagnostics Products Ltd

Summary Number: [redacted] claim #B

Sample Number(s):

Sample Receipt Date:

INTRODUCTION

As described in quote [redacted] claim #B Siemens requested [redacted] claim #B to undertake Triton-X100 content on waste water samples. The results for the samples supplied for testing are as folows.

RESULTS

Client Sample ID	Treatment Site	Date Received	CLS Sample ID	Result % w/v	Pass/Fail
Siemens Original	Llanberis	17-Jul-18	351/001-01	[redacted] #B	Pass
Siemens Original	Llanberis	03-Aug-18	351/001-02 1 of 2		Pass
Siemens Original	Llanberis	03-Aug-18	351/001-02 2 of 2		Pass
Treated Effluent	Llanberis	03-Aug-18	351/001-03 1 of 2		Pass
Treated Effluent	Llanberis	03-Aug-18	351/001-03 2 of 2		Pass
Siemens Original	Llanberis	10-Aug-18	351/001-04 1 of 2		Pass
Siemens Original	Llanberis	10-Aug-18	351/001-04 2 of 2		Pass
Treated Effluent	Llanberis	10-Aug-18	351/001-05 1 of 2		Pass
Treated Effluent	Llanberis	10-Aug-18	351/001-05 2 of 2		Pass
Treated Effluent	Llanberis	17-Aug-18	351/001-06 1 of 2		Pass
Treated Effluent	Llanberis	17-Aug-18	351/001-06 2 of 2		Pass
Siemens Original	Llanberis	17-Aug-18	351/001-07 1 of 2		Pass
Siemens Original	Llanberis	17-Aug-18	351/001-07 2 of 2		Pass
Treated Effluent	Llanberis	24-Aug-18	351/001-08 1 of 2		Pass
Treated Effluent	Llanberis	24-Aug-18	351/001-08 2 of 2		Pass
Siemens Original	Llanberis	24-Aug-18	351/001-09 1 of 2		Pass

Client Sample ID	Treatment Site	Date Received	CLS Sample ID	Result % w/v	Pass/Fail
Siemens Original	Llanberis	24-Aug-18	351/001-09 2 of 2	[redacted]	Pass
Treated Effluent	Marburg	31-Aug-18	351/001-10	[redacted]	Pass
Treated Effluent	Marburg	31-Aug-18	351/001-11	[redacted]	Pass
Treated Effluent	Marburg	31-Aug-18	351/001-12	[redacted]	Pass
Siemens Original	Llanberis	07-Sep-18	351/001-13 1 of 2	[redacted]	Pass
Siemens Original	Llanberis	07-Sep-18	351/001-13 2 of 2	[redacted] #B	Pass
Treated Effluent	Llanberis	07-Sep-18	351/001-14 1 of 2	[redacted]	Pass
Treated Effluent	Llanberis	07-Sep-18	351/001-14 2 of 2	[redacted]	Pass
Siemens Original	Llanberis	07-Sep-18	351/001-15 1 of 2	[redacted]	Pass
Siemens Original	Llanberis	07-Sep-18	351/001-15 2 of 2	[redacted]	Pass
Treated Effluent	Llanberis	07-Sep-18	351/001-16 1 of 2	[redacted]	Pass
Treated Effluent	Llanberis	07-Sep-18	351/001-16 2 of 2	[redacted]	Pass
Siemens Original	Llanberis	14-Sep-18	351/001-17 1 of 2	[redacted]	Pass
Siemens Original	Llanberis	14-Sep-18	351/001-17 2 of 2	[redacted]	Pass
Treated Effluent	Llanberis	14-Sep-18	351/001-18 1 of 2	[redacted]	Pass
Treated Effluent	Llanberis	14-Sep-18	351/001-18 2 of 2	[redacted]	Pass

11.2 Projection of OPE uses

Table 11: Projections of sales of IVD kits and associated use of Triton X-100 in Llanberis

Year	IVD kits sold (global)	OPE amount used (kg)	% of previous year
FY2017		#A	
FY2018	#C	#A	#A
FY2019	#C	#A	#A
FY2020	#C	#A	#A
FY2021	#C	#A	#A
FY2022	#C	#A	#A
FY2023	#C	#A	#A
FY2024	#C	#A	#A
FY2025	#C	#A	#A
FY2026	#C	#A	#A
FY2027	#C	#A	#A
FY2028	#C	#A	#A
FY2029	#C	#A	#A

Source: Siemens Llanberis

Note 1: OPE amount is calculated from volumes (litres), assuming a density of Triton™ X-100 of 1.061 g/ml at 25°C

Note 2: claim #B [redacted]

Figure 11: Projections on use volumes of Triton™ X-100

11.3 Calculation of maximum daily use at Llanberis

11.3.1 Triton™ X-100 usage per typical year

Triton usage within use #1 is divided into 4 types:

[redacted]

[redacted]

(For this estimate, the usage figures for the [redacted] analyte bead are used as this represents worst-case usage)

[redacted]

[redacted]

claim #A [redacted]

Summary

claim #A [redacted]

claim #A [redacted]

Assuming 2 wastewater tanks up to #A **kg OPnEO** may be present in one tank and discharged to Liverpool WwTW within one day.

11.3.2 Estimated development of weekly/daily tonnage 2017 - 2030

Table 12: Estimation of lot numbers and weekly/daily tonnage with decreasing OPnEO use

	FY17 to FY21	FY22 to FY23 (< 2/3 of FY17)	FY24 to FY 25 (< ½ of FY17)	FY26 to FY 29 (< 1/3 of FY 17)	FY30 = 0
maximum weekly volume	#A kg OPnEO	#A kg OPnEO	#A kg OPnEO	#A kg OPnEO	0
maximum daily volume	[redacted] kg OPnEO	[redacted] kg OPnEO	[redacted] kg OPnEO	[redacted] kg OPnEO	0
(1) maximum number of lots TX washed beads	#B	#B	#B	#B	0
(1) maximum volume OPnEO for TX washed beads	#A g OPnEO	#A g OPnEO	#A g OPnEO	#A g OPnEO	0
(2) maximum number of lots claim #B beads	#B	#B	#B	#B	0
(2) maximum volume OPnEO for claim #B beads	#A g OPnEO	#A g OPnEO	#A g OPnEO	#A g OPnEO	0
(3) maximum number of lots claim #B beads	#B	#B	#B	#B	0
(3) maximum volume OPnEO for claim #B beads	#A g OPnEO	#A g OPnEO	#A g OPnEO	#A g OPnEO	0
(4) maximum number of lots claim #B beads	#B	#B	#B	#B	0
(4) maximum volume OPnEO for claim #B beads	#A g OPnEO	#A g OPnEO	#A g OPnEO	#A g OPnEO	0

11.4 Justification for confidentiality claims

Table 13: Justification for confidentiality claims (#A, #B and #C)

Reference type	Commercial Interest	Potential Harm	Limitation to Validity of Claim
[redacted] claim #A [redacted]	[redacted]	[redacted]	[redacted]
[redacted] claim #B [redacted]	[redacted]	[redacted]	[redacted]

Reference type	Commercial Interest	Potential Harm	Limitation to Validity of Claim
[redacted] claim #C [redacted]	[redacted]	[redacted]	[redacted]

11.5 List of Abbreviations

Remark: OPnEO, OPE and Triton™ X-100 are used synonymously

AfA	Application for authorisation
AoA	Analysis of Alternatives
AP	Alkylphenol
APERC	Alkylphenols & Ethoxylates Research Council
APEs	Alkylphenol ethoxylates
APnEC (AP1EC, AP2EC)	Alkylphenol carboxylates
APnEO (AP1EO, AP2EO)	Alkylphenol ethoxylates
dw	Dry weight
ECHA	European Chemicals Agency
ECS	Environmental Contributing Scenario
EDC	Endocrine disrupting chemical
EDS	Endocrine disruptive substance
EQS	Environmental Quality Standard
ERC	Environmental release category within the use descriptor system*
IUCLID	International Uniform Chemical Information Database
MAC-EQS	Environmental Quality Standard expressed as a maximum allowable concentration (short-term EQS)
NP	Nonylphenol
NPnEC (z.B. NP1EC)	Nonylphenol carboxylates
OC	Operation Conditions of use
OP	Octylphenol
OPE	4-(1,1,3,3-Tetramethylbutyl)phenol, ethoxylated
OPnEC	Octylphenol carboxylates
OPnEO	4-(1,1,3,3-Tetramethylbutyl)phenol, ethoxylated
PEC	predicted environmental concentration
PNEC	Predicted no-effect concentration
PROC	Process category within the use descriptor system*
RAC	Risk Assessment Committee
RCR	Risk Characterization Ratio
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RMM	Risk Management Measure
STP	Sewage treatment plant
t-OP	tert-octylphenol
WCS	Workers Constributing Scenario
ww	Wet weight
WHO	World Health Organisation
WWTP	Wastewater treatment plant

* see chapter R.12 in the related ECHA guidance
https://echa.europa.eu/documents/10162/13632/information_requirements_r12_en.pdf/ea8fa5a6-6ba1-47f4-9e47-c7216e180197