CHEMICAL SAFETY REPORT

Legal name of applicant(s):	Roche Diagnostics Limited
Submitted by:	Roche Diagnostics Limited
Substance:	1) 4-(1,1,3,3-Tetramethylbutyl)phenol, ethoxylated (covering well-defined substances and UVCB substances, polymers and homologues); (Octylphenolethoxylates, OPnEO). 2) 4-Nonylphenol, branched and linear, ethoxylated (substances with a linear and / or branched alkyl chain with a carbon number of 9 covalently bound in position 4 to phenol, ethoxylated covering UVCB- and well-defined substances, polymers and homologues, which include any of the individual isomers and / or combinations thereof); (Nonylphenolethoxylates, NPnEO).
Use title:	Use 3: Use of Octyl- and Nonylphenolethoxylates in *in vitro* diagnostic (IVD) assays specified in Appendix 1 to the AoA
Use number:	3

PART A

1. SUMMARY OF RISK MANAGEMENT MEASURES

The risk management measures applicable to the use of Octyl- and Nonylphenolethoxylates for the use of Octyl- and Nonylphenolethoxylates in *in vitro* diagnostic (IVD) assays specified in Annex 1 to the AoA (Analysis of Alternatives) are stipulated in Section 9 of the CSR (Chemical Safety Report). For a summary, please refer to Table 1 (Succinct summary of representative risk management measures (RMMs) and operational conditions (OCs)). For further details, please refer to the relevant sections in Section 9 of the CSR.

2. DECLARATION THAT RISK MANAGEMENT MEASURES ARE IMPLEMENTED

This use applied for (Use 3) does not concern usage by the applicant itself. Therefore, no risk management measures need to be implemented by the applicant.

3. DECLARATION THAT RISK MANAGEMENT MEASURES ARE COMMUNICATED

There are no additional risk management measures other than the ones provided in the communication to customers in relation to the IVD assays (for description of RMMs see Sections 9.4.1.2.2 and 9.5.1.2.2).

Table 1. Succinct summary of representative risk management measures and operational conditions: Exposure Scenario: PW1 – OPnEO / NPnEO - Use in IVD assays for laboratories / hospitals / blood banks

ECS and WCS	**Task (ERC/spERC or PROC)**	**Annual amount per site (kg/a) (sunset date)**	**Technical RMMs, including: *Containment, *Ventilation (general, LEV…) *customized technical installation, etc.**	**Organisational RMMs, including: *Duration and Frequency of exposure *OSH management system *Supervision *Monitoring arrangements *Training, etc.**	**PPE (characteristics)**	**Other conditions**	**Effectiveness of wastewater and waste air treatment (for ERC)**	**Release factors: water, air and soil (for ERC)**	**Detailed info. in CSR (section)**
ECS 1: PW1 – OPnEO	ERC8a	Total UK amount (kg/a): 40.19	n.a. (environmentally hazardous substance)	n.a. (environmentally hazardous substance)	n.a. (environmentally hazardous substance)	n.a. (environmentally hazardous substance)	Wastewater treatment at municipal STP. Effectiveness: 45.5% of $OP_{equiv.}$ No release to air expected due to low volatility. Solid waste is collected and disposed of 'as if it was hazardous waste'.	Water: 84% Air: 0% Soil: 0% (however, 100% of sewage sludge disposed on soil) Waste: 16%	9.4.1
ECS 1: PW1 – NPnEO	ERC8a	Total UK amount (kg/a): 0.39	n.a. (environmentally hazardous substance)	n.a. (environmentally hazardous substance)	n.a. (environmentally hazardous substance)	n.a. (environmentally hazardous substance)	Wastewater treatment at municipal STP. Effectiveness: 75.3% of $NP_{equiv.}$	Water: 47% Air: 0% Soil: 0% (however, 100% of	9.5.1

							No release to air expected due to low volatility. Solid waste is collected and disposed of 'as if it was hazardous waste'.	sewage sludge disposed on soil) Waste: 53%	

Abbreviations: ECS=Environmental Contributing Scenario,* ERC=Environmental Release Category (or spERC= specific Environmental Release Category, if available), PROC= Process category, LEV=Local Exhaust Ventilation, PPE=Personal Protective Equipment, WCS= Worker Contributing Scenario, PW= Professional Worker, EEA= European Economic Area, OSH= Occupational Safety and Health, STP= Sewage treatment plant, $OP_{equiv.}$=4-(1,1,3,3-tetramethylbutyl)phenol Equivalent, NP_{equiv}.= 4-nonylphenol Equivalent, OPnEO=4-(1,1,3,3-tetramethylbutyl) phenol, NPnEO=4-nonylphenol

TABLE OF CONTENTS

TABLES

FIGURES

GLOSSARY

Term	Explanation
AA-EQS	Annual average environmental quality standard
ACS	American Chemical Society
AfA	Application for Authorisation
AIDS	Acquired Immunodeficiency Syndrome
AoA	Analysis of Alternatives
BILT3	Bilirubin Total Gen 3
BIVDA	The British In Vitro Diagnostics Association
CAGR	Compound Annual Growth Rate - the mean annual growth rate of an investment over a specified period of time longer than one year.
CC	Clinical chemistry is a diagnostic method which tests for various components of blood and urine and enables healthcare professionals to overview significance of abnormal values. CC portfolio are part of the Serum Work Area.
CE mark	CE marking proves that your product has been assessed and meets EU safety, health and environmental protection requirements
CEC	Corporate Executive Committee
CESIO	Comité Européen des Agents de Surface et de leurs Intermédiaires Organiques - European Committee of organic surfactants and their organic intermediates
CFDA	China Food and Drug Administration
CH	Switzerland
CHF	Swiss francs
CLIA Waver	CLIA waiver means that this product is waived from Clinical Laboratory Improvement Amendments (CLIA) regulations that regulates laboratory testing and therefore do not require clinical laboratories certification by a state as well as the Centre for Medicare and Medicaid Services (CMS) before they can accept human samples for diagnostic testing.

Term	Explanation
CLP	European Union regulation, which aligns the EU system of classification, labelling and packaging of chemical substances and mixtures. The EU CLP Regulation as amended is retained in the UK law under the SI 720 of 2019.
CMC	Critical micelle concentration
cobas®	Trade name of Roche diagnostic instrument
CPS	Centralised & Point of Care (CPS) is the largest business area of Roche Diagnostics. It is a leading supplier of solutions, instruments, tests, software and services for small- to mid-size and large-size commercial and hospital labs and laboratory networks.
CSF	CerebroSpinal Fluid is a clear, colourless body fluid found in the brain and spinal cord.
CSR	Chemical Safety Report
DIG	Digoxigenin
DJSI	Dow Jones Sustainability Indices. Indices evaluating the sustainability performance of thousands of companies trading publicly and a strategic partner. This is based on an analysis of economic, social and environmental performance of the company. The DJSI family of indices serves as a benchmark for investors who integrate sustainability considerations into their portfolios
DM	Drug Monitoring, that is included in clinical chemistry, specializes in the measurements of levels of therapeutic drugs or narcotic drugs.
DNA	Deoxyribonucleic acid (contains the genetic code of organisms)
DNP	Dinitrophenyl
EBITA	Earnings Before Interest, Taxes, Depreciation, and Amortization It is an accounting measure calculated using a company's net earnings, before interest expenses, taxes, depreciation, and amortization are subtracted, as a proxy for a company's current operating profitability (i.e., how much profit it makes with its present assets and its operations on the products it produces and sells, as well as providing a proxy for cash flow).

Term	Explanation
ECHA	European Chemicals Agency
ECLIA	Electrochemiluminescence immunoassay
ECS	Environmental Contributing Scenario
ED	Emergency department or Endocrine disrupting
EEA	European Economic Area is the area in which the Agreement on the EEA provides for the free movement of persons, goods, services and capital within the European Single Market.
EMEA	Europe, the Middle East and Africa
Enzyme	A substance produced by a living organism which acts as a catalyst to bring about a specific biochemical reaction. Most enzymes are proteins with large complex molecules whose action depends on their particular molecular shape. Some enzymes control reactions within cells and some, such as the enzymes involved in digestion, outside them
EO	EO degree of ethoxylation
EQS	Environment Quality Standard from the EU Water Frame Directive 2013/39/EU
ERC	Environmental Release Category
EU	European Union
EUR	Euros
FDA	US Food and Drug Administration
FTE	Full-Time Equivalents is a unit that indicates the workload of an employed person in a way that makes workloads or class loads comparable across various contexts.
GDP	Gross domestic product
GJ	Gigajoule, unit of energy
Hb	Haemoglobin
HDL	High Density Lipoproteins, commonly referred to as “good cholesterol”

Term	Explanation
HIV	HIV Assay or Human Immunodeficiency Virus
HIV Duo	Newer generation HIV assay which is OPnEO / NPnEO-free
HIVcPT	HIV combi PT assay
HPLC	High Performance Liquid Chromatography
ICU	Intensive care units
IHC	Immunohistochemistry
Ig	Immunoglobulin
IPC	In-Process Control
ISH	*In situ* hybridization which is a technique for identifying specific DNA or RNA sequence or portion within individual cells in tissue sections, providing insights into physiological processes and disease pathogenesis
IT	Information technology
IVD	*In vitro* diagnostic medical devices. IVD products are regulated and defined by the UK Medical Devices Regulations 2002 (as amended) (S.I. 618 of 2002) as a medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment, or system, whether used alone or in combination, and intended by the manufacturer to be used in-vitro for the examination of specimens, including blood and tissue donations derived from the human body, solely or principally for the purpose of providing information: ▪ concerning a physiological or pathological state, or ▪ concerning a congenital abnormality, or ▪ to determine the safety and compatibility of donations, including blood and tissue donations with potential recipients, or ▪ to monitor therapeutic measures; and includes a specimen receptacle but not a product for general laboratory use, unless that product, in view of its characteristics, is specifically intended by its manufacturer to be used for in vitro diagnostic examination.

Term	Explanation
IW	Industrial worker
LAD	Latest Application Date
LDLC	Low density lipoprotein cholesterol, commonly referred to as "bad cholesterol"
log Koc	Organic Carbon-Water Partitioning Coefficient
MAC-EQS	Maximum allowable concentration environmental quality standard
MLS	Managed Laboratory Services
MD	Molecular Diagnostic
MDR	Medical Device Regulations
MDROs	Multidrug-resistant organisms
MHRA	Medicines and Healthcare products Regulatory Agency in UK which regulates medicines, medical devices and blood components for transfusion. It is an executive agency, sponsored by the Department of Health and Social Care
MLS	Managed Laboratory Services
NAD	Nicotinamide Adenine Dinucleotide
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
NOEC	No Observed Effect Concentration
Non-EEA	All countries outside the European Economic Area (EEA).
NP	4-nonylphenol, branched and linear
NP1EC	4-nonylphenoxyacetic acid
NP1EO	Nonylphenolmonoethoxylate
NP2EC	4-nonylphenoxyethoxyacetic acid
NP2EO	Nonylphenoldiethoxylate

Term	Explanation
$NP_{equiv.}$	4-nonylphenol Equivalent
NPnEO	4-nonylphenol, branched and linear, ethoxylated (substances with a linear and / or branched alkyl chain with a carbon number of 9 covalently bound in position 4 to phenol, ethoxylated covering UVCB- and well-defined substances, polymers and homologues, which include any of the individual isomers and / or combinations thereof), 4-NPnEO [Corresponding to entry 43 of Annex XIV of the REACH regulation as defined in regulation 2017/999/EU and entry 43 of Annex 14 of the UK REACH regulation]
NPV	Net Present Value It is a measurement of profit calculated by subtracting the present values (PV) of cash outflows (including initial cost) from the present values of cash inflows over a period of time. Incoming and outgoing cash flows can also be described as benefit and cost cash flows, respectively.
OC	Operational conditions
OEM	Original Equipment Manufacturer
OP	4-(1,1,3,3-tetramethylbutyl)phenol (4-tert-OP)
OP1EC	4-octylphenoxyacetic acid (4-tert-OP1EC)
OP2EC	4-octylphenoxyethoxyacetic acid (4-tert-OP2EC)
$OP_{equiv.}$	4-(1,1,3,3-tetramethylbutyl)phenol Equivalent
OPnEO	4-(1,1,3,3-tetramethylbutyl) phenol, ethoxylated (covering well-defined substances and UVCB substances, polymers and homologues), 4-tert OPnEO [Corresponding to entry 42 of Annex XIV of the REACH regulation as defined in regulation 2017/999/EU and entry 42 of Annex 14 of the UK REACH regulation]
OSH	Occupational safety and health
PBT	Persistent, Bioaccumulative and Toxic

Term	Explanation
PC	Article categories
PCR	Polymerase Chain Reaction It is a technique used in molecular biology to amplify a single copy or a few copies of a segment of DNA across several orders of magnitude, generating thousands to millions of copies of a particular DNA sequence.
PEC	Predicted environmental concentration
PMA	Pre-Market Approval
PNEC	Predicted no-effect concentrations
PP	Protein production processes
PPE	Professional protective equipment
PRO	Test-strips containing one field
PROC	Process category
PVDF	Polyvinylidene fluoride
PW	Professional worker
Q1, Q2, etc.	Quartal 1, Quartal 2, etc.
QALY	Quality adjusted life year
QC	Quality Control
QSAR	Quantitative structure activity relationship
R&D	Research and Development
RAC	Committee for Risk Assessment
RDG - Roche Diagnostics GmbH	Part of the Diagnostic Division of F. Hoffmann-La Roche Ltd. Roche Diagnostics GmbH (RDG) has an extensive portfolio, one aspect of which is the manufacturing of instrument platforms and reagents for the different Roche affiliates worldwide. It is located in Germany (Mannheim and Penzberg).
RDL	Roche Diagnostics Limited (RDL) is the Roche affiliate in the UK selling Roche's IVDs in the UK.

Term	Explanation
RDUK	All Roche affiliates in the UK.
REACH	Regulation on Registration Evaluation, Authorisation and Restriction of Chemicals European Regulation (EC) No 1907/2006 The EU regulation as amended is reflected in the UK REACH under the SI 758 of 2019. UK REACH is a regulation that applies to the majority of chemical substances that are manufactured in or imported into Great Britain (GB) (England, Scotland, Wales).
RMMs	Risk Management measures
RNA	Ribonucleic acid (contains the genetic code of some viruses, for example HIV)
Roche	F. Hoffmann-La Roche Ltd. and its affiliates are collectively referred to as 'Roche'
RTD	Roche Tissue Diagnostics is a business area of Roche Diagnostics. It is the world's leading supplier of tissue-based cancer diagnostics. Its instruments and reagent systems are used in histology, cytology and drug discovery laboratories worldwide.
RT-PCR	Reverse transcription polymerase chain reaction is a variant of polymerase chain reaction (PCR), is a technique commonly used in molecular biology to detect RNA expression
SDG	Sustainable Development Goals
SDS	Safety data sheet
SEA	Socio-Economic Analysis
SEAC	Socio-economic Analysis Committee
SIN list	The SIN (Substitute It Now!) List is a comprehensive database of chemicals likely to be restricted or banned in the EU.
SOP	Standard operating procedure
spERC	Specific Environmental Release Category
STP	Sewage treatment plant

Term	Explanation
SVHC	Substances of Very High Concern A SVHC is a chemical substance (or part of a group of chemical substances) which meets the criteria of art.57 UK REACH
SWA	Serum work area is a segment of Centralized & Point of Care (CPS), which is characterised by modular instruments. This includes immunoassays, clinical chemistry, and Drug Monitoring.
TMPA	Total Mycophenolic Acid
TPA	Tripropylamine
UK RP	UK Responsible Person
UN	United Nations
UVCB	Substance of Unknown or Variable composition, Complex reaction products or Biological materials
US	United States
VLDL	very low-density lipoproteins
VOLY	Value of a Life Year Lost
vPvB	very Persistent very Bioaccumulative
VSCC	Value of a Statistical Case of Cancer
VSL	Value of a Statistical Life
WCS	Worker Contributing Scenario
WHO	World Health Organisation
£	British pound sterling

DECLARATION

We, the Applicant Roche Diagnostics Limited, are aware of the fact that further evidence might be requested by HSE to support the information provided in this document.

Also, we request that the information blanked out in the "public version" of the Chemical Safety Report is not disclosed. We hereby declare that, to the best of our knowledge as of today (17th of May 2022), 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: Catherine Pawan Date, Place: 17th of May 2022

Catherine Pawan, Director of Legal & Compliance

Signature: Amanda Walker Date, Place: 17th of May 2022

Amanda Walker, Director of Quality & Regulatory Affairs

PART B

HAZARD ASSESSMENT OPnEO / NPnEO

Hazard assessment OPnEO

Summary

A detailed assessment was performed and is documented in the supporting document SD1_CSR_Hazard_assessment_OPnEO_RDL_Use3, Section 4.

Section 1 of the CSR: Identity of the substance and physical and chemical properties

Substance identity:

4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated, substance under Annex 14 of UK REACH (entry 42).

For physical and chemical properties, please refer to the supporting document to this CSR:

SD2a_CSR_Model_description_partI_general_RDL_Use3.

Section 4 of the CSR: Environmental fate properties

Please refer to the supporting supporting documents SD1_CSR_Hazard_assessment_OPnEO_RDL_Use3, Section 3, and SD2a_CSR_Model_description_partI_general_RDL_Use3.

Section 7 of the CSR: Environmental hazard assessment

In its note from December 2017 [5], the RAC leaves the decision to the industry to define if a threshold can be derived for the endpoint ‘endocrine disrupting properties for the environment’ of OPnEO and its degradation product (Octylphenol, OP). Because of the uncertainties associated with these specific properties, the applicant decided to assume that no threshold applies for this endpoint as the safest option. This is in line with the decision by the Committee (RAC), that the current state of knowledge of the endocrine disrupting properties, mode(s) of action and effects of 4-tert-OPnEO and OP in the environment is insufficient to determine a threshold. This was based on industry submissions contained in several EU applications for authorisation. Therefore, the applicant will demonstrate emission and risk minimisation in this CSR.

Please refer to the supporting documents SD1_CSR_Hazard_assessment_OPnEO_RDL_Use3, Section 4 and SD2a_CSR_Model_description_partI_general_RDL_Use3.

In this CSR it is assumed that no threshold value can be assigned to the endocrine disrupting substance OP (4-(1,1,3,3-tetramethylbutyl)phenol). Nevertheless, for illustration purposes, as critical concentration level a freshwater predicted no-effect concentrations (PNEC) of 0.034 µg/L derived for endocrine disruptive effects (see supporting document SD1_CSR_Hazard_assessment_OPnEO_RDL_Use3) was used for comparison with predicted/measured concentrations in the aquatic environment.

Hazard assessment NPnEO

Summary

Nonylphenol, branched, ethoxylated (NPnEO) is identified as a substance of very high concern (SVHC) and thus listed in Annex 14 of UK REACH in entry 43. The reason for inclusion in Annex 14 is given as 'equivalent level of concern having probable serious effects to environment', which is attributable to the formation of degradation products (4-nonylphenols, NP) that have endocrine disrupting properties.

As there is no general agreement on whether PNEC can be derived for endocrine disrupting substances or not [2], the safest option for this assessment was to assume that in effect, no threshold value can be assigned to NPnEO or its degradation products.

As no threshold is derived, a detailed hazard assessment is not considered necessary for this CSR. The properties of NPnEO and its degradation products are described in detail in several regulatory reports (see reference list). A short summary is given below.

The most important environmental fate properties of NPnEO and its main degradation products (nonylphenoldiethoxylate (NP2EO), 4-nonylphenoxyethoxyacetic acid (NP2EC), nonylphenolmonoethoxylate (NP1EO), 4-nonylphenoxyacetic acid (NP1EC) and NP) are biodegradation and, due to the high log Koc (Organic Carbon-Water Partitioning Coefficient), adsorption to organic matter [9] (log Pow (n-Octanol-Water Partition Coefficient) values for all substances: see supporting document: SD2a_CSR_Model_description_partI_general_RDL_Use3).

In sewage treatment plants, NPnEO is transformed to short chain nonylphenol ethoxylates (e.g., NP1EO, NP2EO) and their corresponding carboxylates (e.g., NP1EC, NP2EC) as well as NP. Possibly, some mineralisation occurs [3]. NPnEO and its transformation products including NP are considered to be inherently biodegradable since complete mineralisation is low. In surface water, biodegradation of short chain NPnEO to their corresponding carboxylates occurs. In sediment, short chain NPnEO and their carboxylates are transformed to the stable metabolite NP. The high log Koc of NPnEO with low grades of ethoxylation and of the high log Koc of NP lead to their accumulation in organic material in the compartment's sewage sludge, soil and sediment [9].

With respect to environmental hazard, the endocrine disrupting (ED) properties primarily of NP as the main stable metabolite of NPnEO are in focus in this CSR. The evidence for NP's endocrine disruptive properties mainly stems from studies in fish [9]. Evidence for other types of organisms is more limited, less clear or experimentally still further being explored. Therefore, fish populations are currently the most important endpoint in the assessment of potential risks / impacts to the environment. As critical concentration level for endocrine disruptive effects, a PNEC of 0.39 µg/L was derived assuming an assessment factor of 10 on the lowest valid chronic pelagic no observed effect concentration (NOEC), however, without a mechanistic justification [9]. In this CSR it is assumed that no threshold value can be assigned to this endocrine disrupting substance. Nevertheless, for illustration purposes, the newly derived Environment Quality Standard from the EU Water Framework Directive (EQS) value of 0.043 µg/L [4] was used for comparison with predicted/measured concentrations in the aquatic environment.

Section 1 of the CSR: Identity of the substance and physical and chemical properties

Substance identity:

4-Nonylphenol, branched and linear, ethoxylated, substance under Annex 14 of UK REACH (entry 43).

For physical and chemical properties, please refer to the supporting document SD2a_CSR_Model_description_partI_general_RDL_Use3.

Section 4 of the CSR: Environmental fate properties

Please refer to the supporting information to this CSR: supporting document SD2a_CSR_Model_description_partI_general_RDL_Use3.

Section 7 of the CSR: Environmental hazard assessment

In its note from December 2017 [5], the RAC leaves the decision to the industry to define if a threshold can be derived for the endpoint ‘endocrine disrupting properties for the environment’ of NPnEO and its degradation product (Nonylphenol, NP). Because of the uncertainties associated with these specific properties, the applicant decided to assume that no threshold applies for this endpoint as the safest option. This is in line with the decision by the Committee (RAC), that the current state of knowledge of the endocrine disrupting properties, mode(s) of action and effects of 4-NPnEO and NP in the environment is insufficient to determine a threshold. This was based on industry submissions contained in several EU applications for authorisation. Therefore, the applicant will demonstrate emission and risk minimisation in this CSR.

Please refer to the following supporting documents to this CSR:

SD1_CSR_Hazard_assessment_OPnEO_RDL_Use3 and SD2a_CSR_Model_description_partI_general_RDL_Use3.

SUMMARY

The applicant of this authorisation application is Roche Diagnostics Limited (RDL), a UK-based affiliate company of F. Hoffmann-La Roche Ltd. (collectively hereinafter referred to as 'Roche'), which is the leading company in the *in vitro* diagnostic (IVD) market in Europe (EEA) and worldwide. The current CSR was developed to support RDL's application for authorisation to continue the use of two groups of substances octylphenolethoxylates (OPnEO) and nonylphenolethoxylates (NPnEO) in the UK after the sunset date until complete substitution.

UK REACH has been implemented based on the EU REACH regulation including the Annex XIV entries. The group of substances included in this SEA are therefore also listed in Annex 14 of UK REACH in entries 42 (OPnEO) and 43 (NPnEO). As an EU application for authorisation for the same use for these substances was submitted to ECHA before the latest application date (LAD) of the 4th of July 2019, Article 127GA of UK REACH extends the UK LAD/sunset date to the 30th of June 2022. Since the requirements for authorisation under UK REACH were adopted from the EU, the same approach as for the EU dossier is used in this application. Reference is made where applicable to EU requirements and guidance documents.

RDL, as part of the Roche Group is publicly committed to substituting any Substances of Very High Concern (SVHC) from their products if technically possible. RDL is applying for an authorisation to continue the use of Octyl- and Nonylphenolethoxylates (OPnEO / NPnEO) after the sunset date until complete substitution. This CSR presents the exposure assessment for the following Use 3 (The numbering has been kept from the EU application where further uses were applied for):

Use of Octyl- and Nonylphenolethoxylates in *in vitro* diagnostic (IVD) assays specified in Annex 1 to the AoA.

Because of the uncertainties associated with the endocrine disrupting properties of the degradation products of OPnEO / NPnEO and the question whether a threshold can reliably be derived, the applicant demonstrates emission and risk minimisation in this CSR.

The two groups of substances OPnEO and NPnEO are addressed in the same CSR since they can be regarded as a group or category. However, the exposure assessment is provided in separate sections for the two groups of substances OPnEO and NPnEO due to slightly different physico-chemical parameters and available Environmental Quality Standards (EQS).

In this CSR, the applicant provides reliable estimates of environmental exposure in the UK at the downstream user sites with a focus on critical degradation products of OPnEO and NPnEO i.e. Octylphenol (OP)/ Nonylphenol (NP). The environmental exposure assessment is based on data collected from the downstream user sites to estimate release into the wastewater treatment plant (STP). Exposure estimation to all relevant environmental compartments is calculated with the 'Multifate' model reflecting the degradation mechanism specific to OPnEO / NPnEO. The predicted environmental concentrations (PECs) estimated with the 'Multifate' model for OPnEO / NPnEO and their expected degradation products including OP / NP are all converted to equivalents of OP / NP in agreement with the note of the Risk Assessment Committee (RAC) of December 2017.

In addition, this CSR shows that the exposure to the environment with regard to the use of OPnEO / NPnEO is being reduced over the time as much as technically and practically feasible and that the risks related to the continued use of OPnEO / NPnEO are minimised.

For the purpose of the exposure assessment, the combined estimation of the local release per site and regional release (wide dispersive use) is performed thereby reflecting the interrelation of the activities per site covering the use applied for. In the present CSR, Use 3, i.e. the use in IVD assays, is described. The combined exposure is also reported in the present document in Section 10.

Even though, strictly speaking, a risk characterisation is not possible when considering the endocrine disruptor properties of OPnEO / NPnEO as a non-threshold endpoint, the combined exposure per site is compared with available reference values such as the available EQS data as supporting information.

9. EXPOSURE ASSESSMENT

9.1. Introduction

- ⇨ In this CSR, the applicant provides **reliable estimates of environmental exposure to OPnEO and NPnEO and their degradation products** in the UK based on releases from the downstream user sites.
- ⇨ Data was collected on the operational conditions of the specific IVD assays and instruments to estimate release of OPnEO and NPnEO to wastewater. Exposure was calculated with the **'Multifate' model** which reflects the degradation mechanism specific to OPnEO and NPnEO.
- ⇨ **Exposure to the environment** with regard to the use of OPnEO and NPnEO **is being reduced** as much as technically and practically feasible:
  - Until the EU sunset date by RMMs (disposal of unused product as waste),
  - Over the course of the review period by planned substitution by alternative substances.
- ⇨ **Risks** related to the continued use of OPnEO and NPnEO **can thus be considered as minimised.**

The current CSR was developed to support RDL's application for authorisation to **continue the use of the two groups of substances Octylphenolethoxylates (OPnEO) and nonylphenolethoxylates (NPnEO) after the sunset date until complete substitution in the UK to meet the requirements of UK REACH.** It is based on the CSR developed for a similar application that has previously been submitted by Roche Diagnostics GmbH (RDG) in the EU[1]. RDG is the producer or importer into the EU of the IVD assays covered in this application. All concerned IVD assays are delivered by RDG to RDL for sales in the UK.

OPnEO and NPnEO were included in Annex XIV (entries 42 and 43) of the Regulation on Registration Evaluation, Authorisation and Restriction of Chemicals (REACH) regulation by the European Chemicals Agency (ECHA) because of the endocrine disrupting properties of their degradation products for the environment with a sunset date of the 4th of January 2021. UK REACH has been implemented based on the EU REACH regulation including the Annex XIV entries. The group of substances included in this CSR are therefore also listed in Annex 14 of UK REACH in entries 42 (OPnEO) and 43 (NPnEO). As an EU application for authorisation for the same use for these substances was submitted to ECHA before the latest application date (LAD) of the 4th of July 2019, Article 127GA of UK REACH extends the UK LAD/sunset date to the 30th of June 2022. Since the requirements for authorisation under UK REACH were adopted from the EU, the same approach as for the EU dossier is used in this application. Reference is made where applicable to EU requirements and guidance documents.

[1] Links to the submitted EU Dossier (both links lead to the same dossier):

Link for OPnEO: https://echa.europa.eu/applications-for-authorisation-previous-consultations/-/substance-rev/45043/del/200/col/synonymDynamicField_1512/type/asc/pre/2/view

Link for NPnEO: https://echa.europa.eu/applications-for-authorisation-previous-consultations/-/substance-rev/45044/del/200/col/synonymDynamicField_1512/type/asc/pre/2/view

RDG requested a review period of 7 years after the EU REACH Sunset date (the 4th of January 2021) to authorise the use of OPnEO and/or NPnEO until complete replacement of these substances in all affected IVD products (19 products), i.e. until the 4th of January 2028. For this application for authorisation under UK REACH (10 products), the end of the review period remains the same as substitutions are still planned to be completed by this date. The review period applied for is therefore (approximately) 5.5 years from the 30th of June 2022 till the 4th of January 2028. To simplify, the term 'end of 2027' is used within the text in the EU Dossier to determine the end of the review period. This terminology is also used in this application by RDL.

In its note from December 2017 [5], the Risk Assessment Committee leaves the decision to the industry to define if a threshold can be derived for the endpoint 'endocrine disrupting properties for the environment' for OPnEO / NPnEO and their degradation products. Because of the uncertainties associated with these specific properties, the applicant decided to assume that no threshold applies for this endpoint as the safest option. This is in line with the decision by the Committee (RAC), that the current state of knowledge of the endocrine disrupting properties, mode(s) of action and effects of OPnEO / NPnEO in the environment is insufficient to determine a threshold. This was based on industry submissions contained in several EU applications for authorisation. Therefore, the applicant demonstrates risk/ emission minimisation in this CSR.

The two groups of substances OPnEO and NPnEO are addressed in the same dossier since the ECHA Guidance on the preparation of an application for authorisation, Annex 1 [6] concludes that if the substances were treated as a group or category or a read-across was conducted in the EU REACH Annex XV dossier of the substances, a reference to the Annex XV dossier in the application for authorisation (AfA) is sufficient for the substances to be regarded as a group or category. In the annex XV dossier for OPnEO [8], data on NPnEO are referenced in many instances (e.g. degradation, endocrine effects of the degradation product OP and NP and other endpoints). OPnEO and NPnEO are identified as 'close analogues' and are structurally very similar (OPnEO: $C_{14}H_{22}O[C_2H_4O]_n$ / NPnEO: $C_{15}H_{24}O[C_2H_4O]_n$). Furthermore, they are employed for the same or similar uses in the framework of this AfA. Hence, based on the above stated reasons, OPnEO and NPnEO can be regarded as a group in the AfA and a combined dossier is prepared. However, separate exposure scenarios were developed for the two groups of substances in the CSR due to slightly different physico-chemical parameters and EQS for the two groups of substances. The same approach was used in the EU AfA.

In this CSR, the applicant provides reliable estimates of environmental exposure in the UK at downstream users. In the RAC note from December 2017 [1], RAC indicated that the focus should be the minimisation of the release of OPnEO / NPnEO to the environment with a focus on critical degradation products i.e. Octylphenol (OP, $C_{14}H_{22}O$) / Nonylphenol (NP, $C_{15}H_{24}O$) and that risk to human health did not need to be assessed for the purpose of the exposure assessment. Therefore, exposure of workers, consumer and of man via the environment was considered out of scope for the assessment.

The environmental exposure assessment was based on data collected on the IVD assays and instruments to estimate release into STPs. Exposure estimation to all relevant environmental compartments were calculated with the 'Multifate' model [10]. This model reflects the degradation mechanism specific to OPnEO / NPnEO that would not be considered when using the standard EUSES model [11] (European Union System for the Evaluation of Substances, version 2.0. National Institute of Public Health and the Environment (RIVM), the Netherlands). In agreement with the RAC note of December 2017 [5], the PECs estimated with the 'Multifate' model for OPnEO / NPnEO and its expected degradation products including OP / NP were all converted to equivalents of OP / NP.

This is based on the assumption that all OPnEO / NPnEO released to the environment ultimately ends up as OP / NP.

In addition, this CSR aims to show that the exposure to the environment regarding the use of OPnEO / NPnEO is being reduced over the time as much as technically and practically feasible and that the risks related to the continued use of OPnEO / NPnEO can be considered as minimised. In this context, the achieved decrease of the releases due to the implementation of risk management measures and substitutions planned to be completed from the time of the application date until the end of the review period is provided in Section 9.4.2 of the CSR.

Even though, strictly speaking, a risk characterisation is not possible when considering the endocrine disrupting properties of OPnEO / NPnEO as a non-threshold endpoint, a comparison with available reference values such as the EQS data is presented in Section 10 as supporting information.

OPnEO and NPnEO are used in a wide array of IVD assays. For the EU application for authorisation, three distinct uses were identified within RDG and one further use was identified in the Roche Pharmaceuticals Division (see Table 2). For RDL, only Use 3, the use of the IVD assays at downstream user level is relevant. Therefore, this application refers only to the 'Use of Octyl- and Nonylphenolethoxylates in IVD assays specified in Annex 1 to the AoA'. Please note that some product groups (Roche Molecular Diagnostics, Blood gas and electrolyte, Urinalysis and Accutrend®) that were covered in Use 3 of the EU AfA are not covered in this application as OPnEO / NPnEO is replaced or they are not sold anymore. Further, some products of the product groups Clinical Chemistry (CC) and Drug Monitoring (DM) are not covered in this application because they do not fall under the obligation for authorisation or because OPnEO or NPnEO have already been replaced. Overview of the uses covered in the EU application of authorisation and the use relevant for this AfA is provided in the Table 2 below. Please note that the use applied for in this authorisation dossier depends on RDG receiving the EU authorisation, in particular for Use 2, for actually producing the assays. Table 3 gives an overview of product groups and exposure scenarios within Use 3.

Table 2. Uses overview of the EU AfA and relevant use for this application

Use	Division	User	Short name	Use Name
1	Pharmaceuticals	RDG	Pharma	Use of Octylphenolethoxylates as an emulsifier in the siliconisation of glass containers used as primary packaging for medicinal products (NeoRecormon® and MIRCERA®)
2	Diagnostics	RDG	Formulation	Use of Octyl- and Nonylphenolethoxylates in the formulation and filling of *in vitro* diagnostic (IVD) assays specified in Appendix 1 to the AoA
3	**Diagnostics** **Only use relevant for Roche Diagnostics**	**Downstream Users (e.g. laboratories)**	**Product**	**Use of Octyl- and Nonylphenolethoxylates in *in vitro* diagnostic (IVD) assays specified in Appendix 1 to the AoA**

Use	Division	User	Short name	Use Name
	Limited in the UK			
4	Diagnostics	RDG	Processes	Use of Octyl- and Nonylphenolethoxylates in the production of proteins and the conjugation of latex beads, both being used as components or for the production of components of *in vitro* diagnostic (IVD) assays, research or quality control products and other, e.g. analytical applications (processes specified in Appendix 1 to the AoA)

Table 3. Overview of exposure scenarios, product groups and products within Use 3. Product numbering (e.g. 'CC3') is the same as applied in the EU dossier. The product HIV consists of two reagents (R0 and R1), which are counted as one product.

Exposure scenarios	Product Group	Abbreviation	Products
ES1 OPnEO	Clinical chemistry	CC	**CC3** **CC7**
	Drug Monitoring	DM	**DM5** **DM6** **DM8** **DM9** **DM11**
	Roche Tissue Diagnostic	RTD	**RTD**
ES1 NPnEO	Drug Monitoring	DM	**DM7**
	HIV	HIV	**HIV (R0)** **HIV (R1)**

9.2. Overview of Exposure Scenarios

- ⇨ **Downstream sites such as laboratories and hospitals** purchase IVD assays with reagents containing OPnEO / NPnEO from RDL for the measurements of clinical chemistry, drug monitoring etc., i.e. for diagnostic purposes in healthcare.
- ⇨ The **maximum annual usage** at the UK sunset date for Use 3 was estimated to be **40.19 kg/a OPnEO and 0.39 kg/a NPnEO**.
- ⇨ However, the total annual usage of OPnEO and NPnEO is expected to decrease over time due to **completed substitutions** of OPnEO and NPnEO in the formulation and in the corresponding downstream products. Two cases are shown in the dossier:
  - 'All substitutions completed as planned': If the substitutions in the formulated reagents are completed as planned, the total annual amount of OPnEO will be 1.4 g/a on 1st of June 2025 (0 g/a on 1st of April 2026) and NPnEO will reach 0 g/a by the end of 2027 for the use applied for.
  - 'All substitutions delayed': If the substitutions are delayed, a maximum total annual amount of 48.65 kg/a OPnEO by the end of 2027 could potentially be reached based on sales development and usage could continue until the end of the review period (4th of January 2028). For NPnEO the usage will constantly decrease after the UK sunset date, even if the substitutions are delayed.
- ⇨ RDL therefore applies for a **maximum annual amount of 48.65 kg/a of OPnEO and 0.39 kg/a NPnEO** for Use 3.

9.2.1. Use Applied For

An AfA is submitted by RDL for Use 3 for downstream activities taking place at hospitals, laboratories, and blood banks for the two groups of substances OPnEO and NPnEO. Please note that in the following text we only refer to 'hospitals / laboratories', which includes the blood banks (except in Sections 9.5.1.2.4 and 10.2 where blood banks are specifically addressed).

9.2.2. Overview of Exposure Scenarios and Mass Balances – OPnEO

RDL imports IVD assays containing OPnEO which are sold to and used by UK customers such as at laboratories / hospitals (Exposure Scenario 1 - PW1[1] – OPnEO).

9.2.2.1. Overview of Exposure Scenarios – OPnEO

An overview of the exposure scenario currently falling in the scope of RDL's authorisation application for OPnEO for Use 3 is provided in Table 4 (Exposure Scenario 1 - PW1[1] – OPnEO). Note that the amounts given in Table 4 only refer to uses that are subject to authorisation. The amount is given at the UK sunset date and, in addition, the maximum annual amount is given that could be reached until the end of the review period as a worst-case if all substitutions are delayed. In both cases, i.e. on time and delayed substitutions, the usage at the UK sunset date is the same, as for all products the shelf life would still be running.

RDL is therefore applying for an annual usage of this maximum of 48.65 kg/a OPnEO.

Table 4. Overview of exposure scenarios and contributing scenarios for OPnEO.

Identifiers*	Market Sector	Titles of exposure scenarios and the related contributing scenarios	Amount at UK sunset date (kg per year)	Maximum annual amount applied for, end of 2027 (kg per year)
PW1 – OPnEO	SU 20: Health services PC0: IVD assays PC 21: Laboratory chemical	Use in IVD assays at laboratories / hospitals Professional use PROC15 – Use as laboratory reagent ERC8a – Wide-dispersive indoor use of processing aids in open systems	40.19 kg/a	48.65 kg/a

***** Professional end use: PW-#

9.2.2.2. Mass Balances and Evolution of Used Amounts over Time – OPnEO

From the UK sunset date on the 30th of June 2022 till the end of the review period, the total used amounts of OPnEO at downstream sites is expected to vary mainly due to:

- Increase in quantities of OPnEO required for the IVD assays due to sales development of IVD – assays, and consequently of the quantities of OPnEO used by the downstream users (laboratories / hospitals).

- Planned substitutions of OPnEO in the IVD assays leading to a decrease of OPnEO used at the downstream users.

For the purpose of the CSR, the maximum annual usage for Use 3 at the end of 2027, assuming that all substitutions are delayed, serves as a basis for the exposure assessment as this represents a worst-case of the used amounts. The total annual usage in the UK, including the predicted development over the review period, are based on the figures given in the AfA submitted by RDG in the EU. For the EU dossier, the sales figures for the different IVD assays for 2016-2017 sold to the different European Economic Area (EEA) downstream users i.e. laboratories / hospitals and data on export into non-EEA countries were collected. Note that for the present dossier the figures were adapted to only represent the product groups and assays in scope of this UK AfA and were scaled to the UK (see further information below). The figures were verified and represent a reasonable estimate since the business for the assays covered in this AfA has not substantially changed since the preparation of the EU dossier. Further, the situation on the UK market is comparable to the situation in the EU (including the UK) as described in the EU dossier.

At the time of preparing the EU dossier, the expected sales development between 2017 and 2022 translated into corresponding amounts and/or direct volume predictions was considered in the estimates. They are further scaled to the UK market using the percentage of the total number of instruments considered in the EU dossier (EEA including the UK) that are installed in the UK. This

is a reasonable approximation since (liquid and solid) waste generation mainly depends on the use of assays and the use of assays per instrument can be assumed to be on average the same.

These data were then aggregated per exposure scenario and served as a basis for the estimation of the total annual usage at the downstream users at the UK sunset date considering the expected development until the 30th of June 2022 based on 2016/1017 data. This estimation was further extrapolated to the end of the review period (the 4th of January 2028) considering the development in the sales figures and/or volume predictions as forecasted until the end of 2027 (see Figure 1).

The total annual usage of OPnEO for the downstream sites will further increase after the UK sunset date due to growth in the sales figures. However, total annual usage of OPnEO is expected to decrease from 2024 to reach 0 at the latest at the end of the review period due to completed substitutions of OPnEO in the IVD assays. The maximum amount over the review period is used as a basis for the exposure assessment as a worst-case. This maximum amount is 22% higher compared to the usage at the UK sunset date (Table 4).

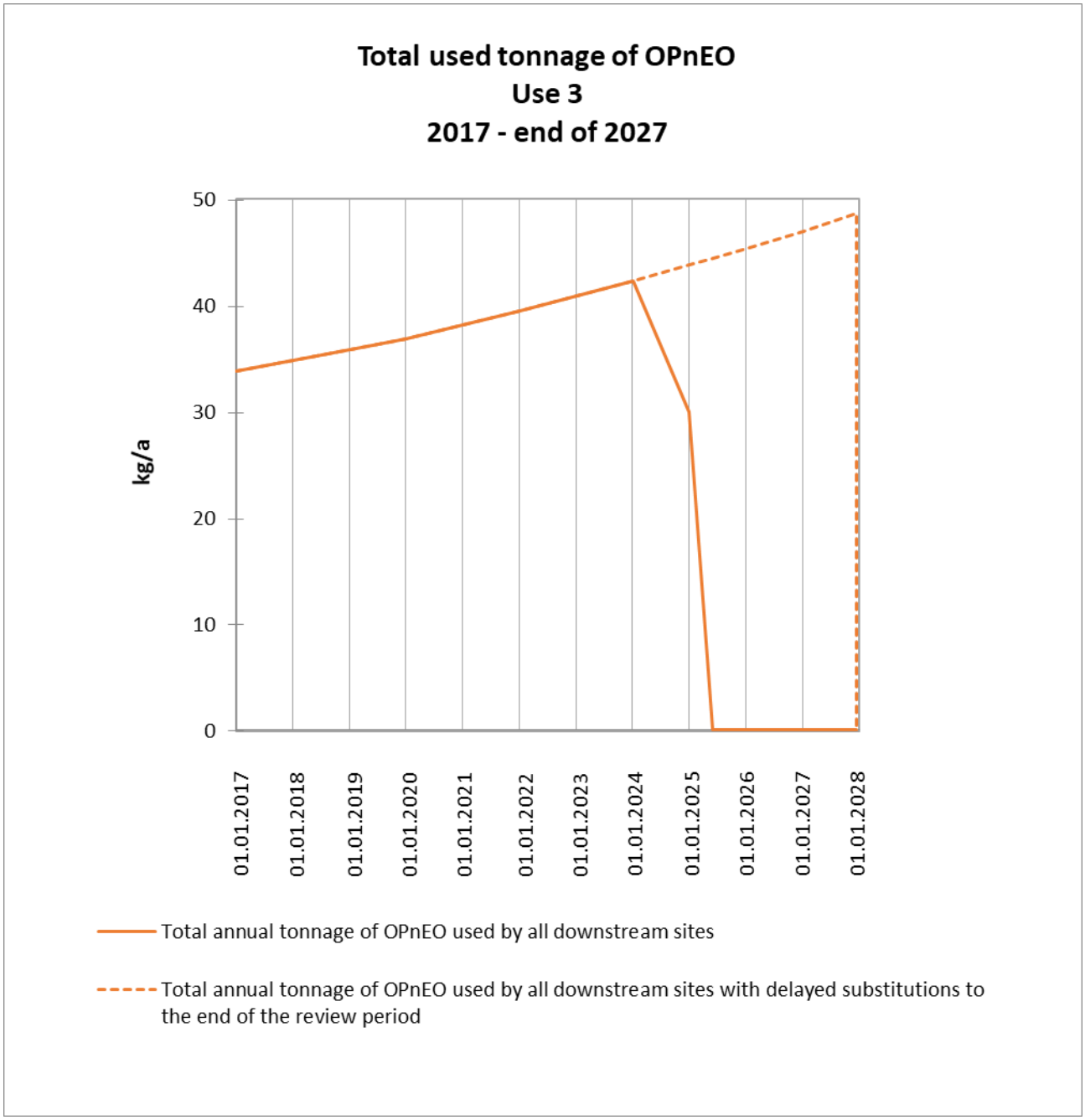

Figure 1. Evolution of the total annual use of OPnEO between 2017 and end of 2027 for the downstream users' sites considering planned substitutions and sales development.

Figure 1 provides an overview of the expected evolution in the total used amount of OPnEO over time for usage of the IVD assays at downstream sites considering the development in the sales figures for two cases:

- 'All substitutions completed as planned': Expected decrease in the total used amount of OPnEO after 1st of January 2024 considering the planned substitutions at the production sites and subsequent phase-out and replacement of the products at the downstream users' sites depending on shelf life of the products (see AoA for details).

- 'All substitutions delayed': Expected development of total used amount of OPnEO over time considering that all planned substitutions at the production sites and subsequent phase-out and replacement of the products at the downstream users' sites are delayed to the end of the review period as a worst-case.

At the downstream sites, the total annual amount of OPnEO will initially increase from 40.19 kg/a at the UK sunset date to 42.28 kg/a on 1st of January 2024 due to growth in the sales figures. After this date, the used amount will start to decrease and reach 1.4 g/a on 1st of June 2025 (0 g/a on 1st of April 2026) if the substitutions are completed in time in the formulated reagents. This is in-line with the delay due to the shelf life of the products. However, if the substitutions are delayed towards the end of the review period for all formulation activities, a maximum annual usage of 48.65 kg/a from all uses at the downstream sites could potentially be reached as a worst-case until the end of the review period.

In addition, a mass balance for OPnEO based on amounts used by downstream sites and releases to wastewater is provided in Table 5. Note that the amounts given in Table 5 only refer to uses that are subject to authorisation. The values are provided for the UK sunset date in 2022. Further, the maximum annual amount is given that could be reached until the end of the review period as a worst-case if all substitutions are delayed (amount applied for). Any losses to the environment of the OPnEO used per year is linked with the release to the surface water from STP, release to soil via application of sludge or release from landfills after waste disposal. There is no direct release of OPnEO to air / soil.

Table 5. Mass balance for OPnEO based on amounts used by downstream users' sites and calculated releases to wastewater and waste for the UK sunset date on the 30th of June 2022 and maximum annual amount that could be reached until the end of the review period (end of 2027).

		Annual amount at UK sunset date on the 30th of June 2022	**Maximum annual amount applied for, end of 2027**
		kg/a	**kg/a**
Total for all laboratories / hospitals	**Total annual amount** (total amount imported from EEA)	**40.19**	**48.65**
	Total release to wastewater	**33.33**	**40.77**
	Total amount disposed of as waste	6.86	7.88

9.2.3. Overview of Exposure Scenarios – NPnEO and Mass Balance

RDL imports IVD assays containing NPnEO which are sold to and used by UK customers such as at laboratories / hospitals / blood banks (Exposure Scenario PW1 – NPnEO).

9.2.3.1. Overview of Exposure Scenario – NPnEO

An overview of the exposure scenario currently falling in the scope of the application for authorisation of RDL for NPnEO for Use 3 is provided in Table 6 (Exposure Scenario PW1 – NPnEO). Note that the amounts given in Table 6 only refer to uses that are subject to authorisation. The amount is given at the UK sunset date assuming that all substitutions are delayed. The maximum annual amount over the course of the review period is reached at the UK sunset date. After this date, the usage will constantly decrease, even if the substitutions are delayed.

RDL is therefore applying for an annual usage of this maximum of 0.39 kg/a NPnEO.

Table 6. Overview of exposure scenarios and contributing scenarios for NPnEO.

Identifiers*	**Market Sector**	**Titles of exposure scenarios and the related contributing scenarios**	**Amount at UK sunset date (kg per year)**	**Maximum annual amount applied for, at UK sunset date (kg per year)**
PW1 - NPnEO	SU 20: Health services PC0: IVD assays PC 21: Laboratory chemical	Use in IVD assays at laboratories/ hospitals/ blood banks Professional use PROC15 - Use as laboratory reagent ERC8a - Wide-dispersive indoor use of processing aids in open systems	0.39 kg/a	0.39 kg/a

***)** Manufacture: M-#, Formulation: F-#, Industrial end use at site: IW-#, Professional end use: PW-#, Consumer end use: C-#, Service life (by workers in industrial site): SL-IW-#, Service life (by professional workers): SL-PW-#, Service life (by consumers): SL-C-#.)

9.2.3.2. Mass Balances and Evolution of Used Amounts over Time – NPnEO

From the UK sunset date on the 30th of June 2022 till the end of the review period, the total used amounts of NPnEO at downstream sites is expected to vary mainly due to:

- Decrease in quantities of NPnEO required for the IVD assays due to sales development of IVD assays and consequently of the quantities of NPnEO used by the downstream users (laboratories / hospitals / blood banks),
- Planned substitutions of NPnEO in the IVD assays leading to a decrease of NPnEO used at the downstream users.

For the purpose of the CSR, the total annual usage at the UK sunset date for Use 3 assuming that all substitutions are delayed serves as a basis for the exposure assessment. The total annual usage in the UK, including the predicted decrease over the review period, are based on the figures given in the AfA submitted by RDG in the EU. For the EU dossier, the sales figures for the different IVD assays for 2016-2017 sold to the different EEA downstream users i.e. laboratories / hospitals and data on export into non-EEA countries were collected. Note that for the present dossier the figures were adapted to only represent the product groups and assays in scope of this UK AfA and were scaled to the UK (see further information below). The figures were verified and represent a reasonable estimate since the business for the assays covered in this AfA has not substantially changed since the preparation of the EU dossier and the situation on the UK market is comparable to the situation in the EU (including the UK) as described in the EU dossier.

Please note that this is applicable with the exception of HIV. Current figures were collected and assessed for HIV since the situation on the UK market regarding the replacement of instruments with new generation instruments for HIV differed substantially from what was described for the EU market. However, to improve readability of the document, the exception of HIV will not be mentioned in the further text each time we refer to the data basis of the calculations.

At the time of preparing the EU dossier, the expected sales development between 2017 and 2022 translated into corresponding amounts and/or direct volume predictions was considered in the estimates. They are further scaled to the UK market using the percentage of the total number of instruments considered in the EU dossier (EEA including the UK) that is installed in the UK. This is a reasonable approximation since (liquid and solid) waste generation mainly depends on the use of assays and the use of assays per instrument can be assumed to be on average the same.

These data were then aggregated per exposure scenario and served as a basis for the estimation of the total annual usage at the downstream users at the UK sunset date considering the expected development until the 30th of June 2022. This estimation was further extrapolated to the end of the review period (the 4th of January 2028) considering the development in the sales figures and/or volume predictions as forecasted until the end of 2027 (see Figure 2).

However, the total annual usage of NPnEO for the downstream sites is expected to decrease overtime from the UK sunset date to reach 0 at the latest at the end of the review period due to completed substitutions of NPnEO in the IVD assays and replacement with new generation instruments for HIV. Therefore, the maximum amount at the sunset date is used as a basis for the exposure assessment (Table 6).

Figure 2 provides an overview of the expected decrease in the total used amount of NPnEO over time for usage of the IVD assays at downstream sites considering the development in the sales figures for two cases:

- ‘All substitutions completed as planned’: Expected decrease in the total used amount of NPnEO over time considering the planned substitutions at the production sites and subsequent phase-out and replacement of the products at the downstream users‘ sites depending on shelf life of the products (see AoA for details).

- ‘All substitutions delayed’: Expected development of total used amount of NPnEO over time considering that all planned substitutions at the production sites and subsequent phase-out and replacement of the products at the downstream users’ sites are delayed to the end of the review period as a worst-case.

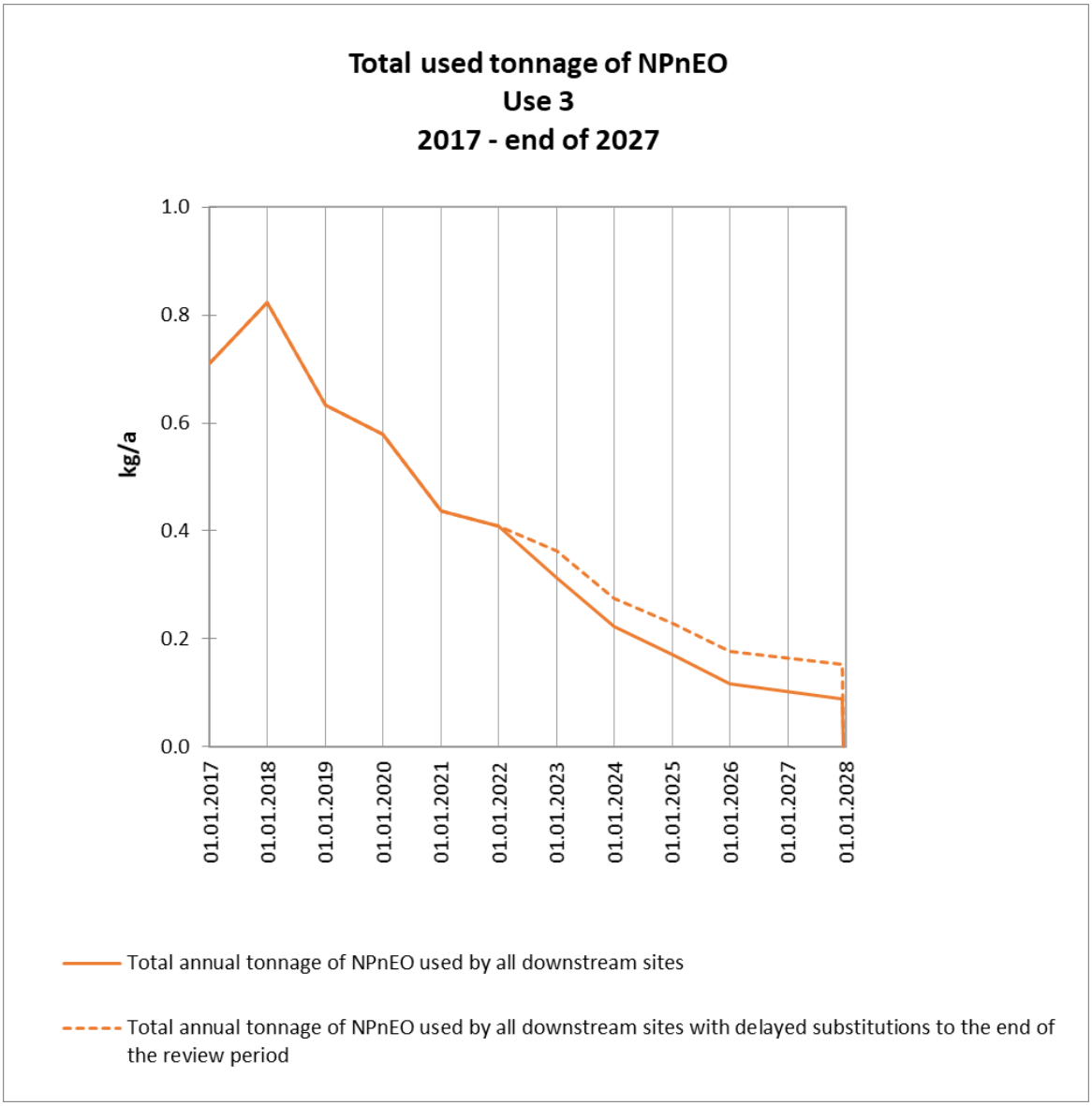

Figure 2. Evolution of the total annual used of NPnEO between 2017 and end of 2027 for the downstream user's sites considering planned substitutions and sales development.

At the downstream sites, the total annual amount of NPnEO should decrease from 0.36 kg/a at the UK sunset date to cease until the end of 2027 if the substitutions are completed in time in the formulated reagents. This is in-line with the delay due to the shelf life of the products. However, if the substitutions are delayed towards the end of the review period for all formulation activities, a total annual usage of 0.39 kg/a from all uses at the downstream sites could potentially be reached at the UK sunset date as a worst-case. The maximum usage of 0.39 kg/a would be reached at the UK sunset date in case of delayed substitutions.

In addition, a mass balance for NPnEO based on amounts used by downstream sites and releases to wastewater is provided in Table 7. Note that the amounts given in Table 7 only refer to uses that are subject to authorisation. The values are provided for the UK sunset date based on the assumption that all substitutions are delayed (worst-case). The amount at the UK sunset date corresponds to the maximum annual amount applied for. Any losses to the environment of the NPnEO used per year is

linked with the release to surface water from STP, release to soil via application of sludge or release from landfills after waste disposal. There is no direct release of NPnEO to air / soil.

Table 7. Mass balance for NPnEO based on amounts used by downstream users' sites and calculated releases to wastewater and waste for the UK sunset date 30th of June 2022 based on the assumption that all substitutions are delayed.

		Annual amount at UK sunset date 30th of June 2022 (worst-case)	**Maximum annual amount applied for, UK sunset date**
		kg/a	**kg/a**
Total for all hospitals / laboratories	**Total annual usage** (total amount imported from EEA)	**0.39**	**0.39**
	Total release to wastewater	**0.18**	**0.18**
	Total amount disposed of as waste	0.21	0.21

9.3. Introduction to the Assessment

- ⇨ The releases of OPnEO and NPnEO occur **via the release to wastewater from the laboratories or hospitals to municipal STPs.**
- ⇨ **The total annual usage in the UK**, including the predicted development over the review period, is based on the figures given in the AfA submitted by RDG in the EU. These typically included data on the total amount of substances used per year per IVD assay, number of assays per average laboratory, maximum number of assays in a big laboratory, fractions being disposed as waste. Subsequently, these data were scaled to the UK market using the percentage of the total number of instruments (EEA and the UK) installed in the UK.
- ⇨ **PECs were calculated using the 'Multifate' model** based on collected data considering RMMs implemented by the EU sunset date (the 4th of January 2021) and assuming wide-dispersive use and standard STP parameters.
- ⇨ Expected biodegradation products including OP / NP were converted to **$OP_{equiv.}$ and $NP_{equiv.}$**, respectively.
- ⇨ **Calculated PECs were compared with available reference values** (EQS values from the Water Framework Directive (Standards and Classification) Directions (England and Wales) 2015) and monitoring data from the literature as supporting information.

9.3.1. Description of the Activities Covered in the Exposure Scenarios

In the following, the usage of the IVD assays in laboratories or hospitals is described including the generation of waste and handling of such waste. Usage at blood banks is comparable to laboratories and hospitals. Therefore, the following description also applies to blood banks. As usage is the same for assays both with OPnEO or NPnEO, this description covers both substances. Figure 3 presents a very general scheme of the typical use of reagents in IVD assays taking place at a laboratory / hospital.

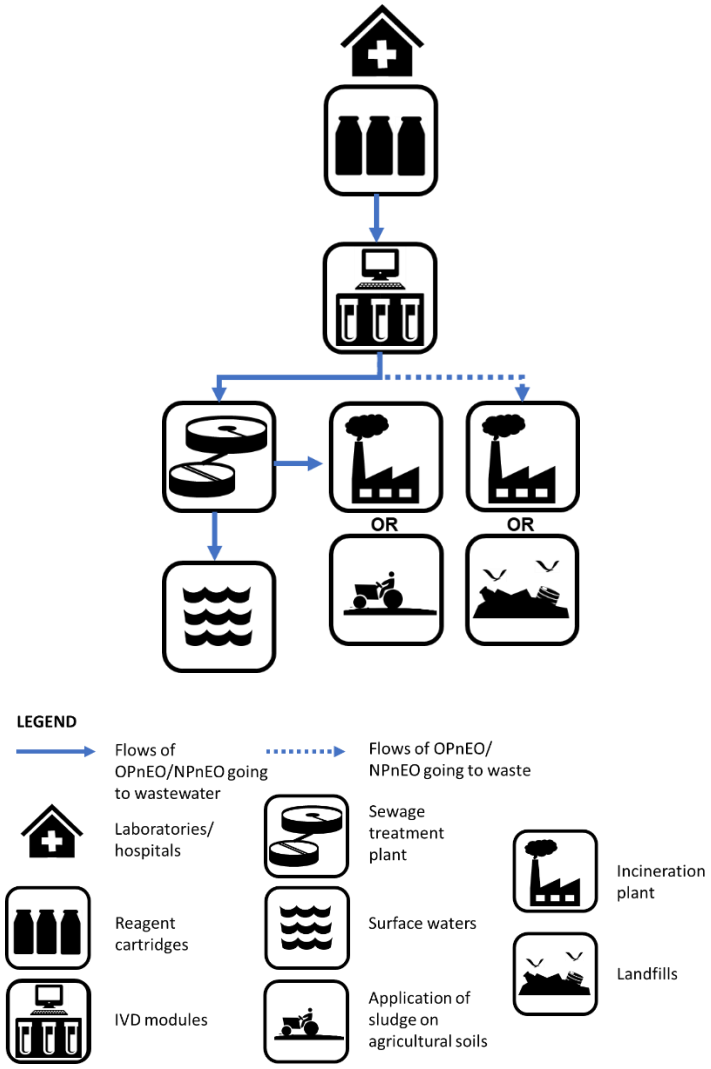

Figure 3. Flows of OPnEO / NPnEO during the typical use of reagents in IVD assays taking place at a laboratory/hospital.

Laboratories and hospitals purchase IVD assays with reagents containing OPnEO / NPnEO from RDL for the measurements of clinical chemistry, drug monitoring, HIV or tissue staining i.e. for diagnostic purposes in healthcare (for more details see SEA section 2.7 Overview of Products).

For CC/DM or HIV assays, laboratories and hospitals receive different types of reagents in form of small cartridges which may contain up to 3 different reagents (see Figure 4). These cartridges are typically directly inserted as such in the corresponding slot of the IVD instrument (examples of IVD instruments: see Figure 5). Laboratory staff are therefore not in contact with the reagents. From there, the different reagents required for the analyses are automatically pumped and pipetted to the samples to allow the reaction to occur. Once the reaction is completed, the samples are analyzed differently depending on the parameter being measured. During the test – depending on the test and the instrument – liquid (such as used reagents) and / or solid waste (such as the empty cartridges) is being generated. The OPnEO / NPnEO from the reagents is present in all of these waste fractions.

For RTD, laboratories and hospitals receive the wash buffer as a 10x pre-concentrate which is then diluted with water to a working 2x solution. The 2x solution is placed on the instrument in a carboy

and is applied to applicable slides via the automated fluidics module on the instrument. The wash buffer is contained in the liquid waste from the instruments.

Figure 4. Example of cartridges containing formulated reagent used at the laboratories / hospitals.

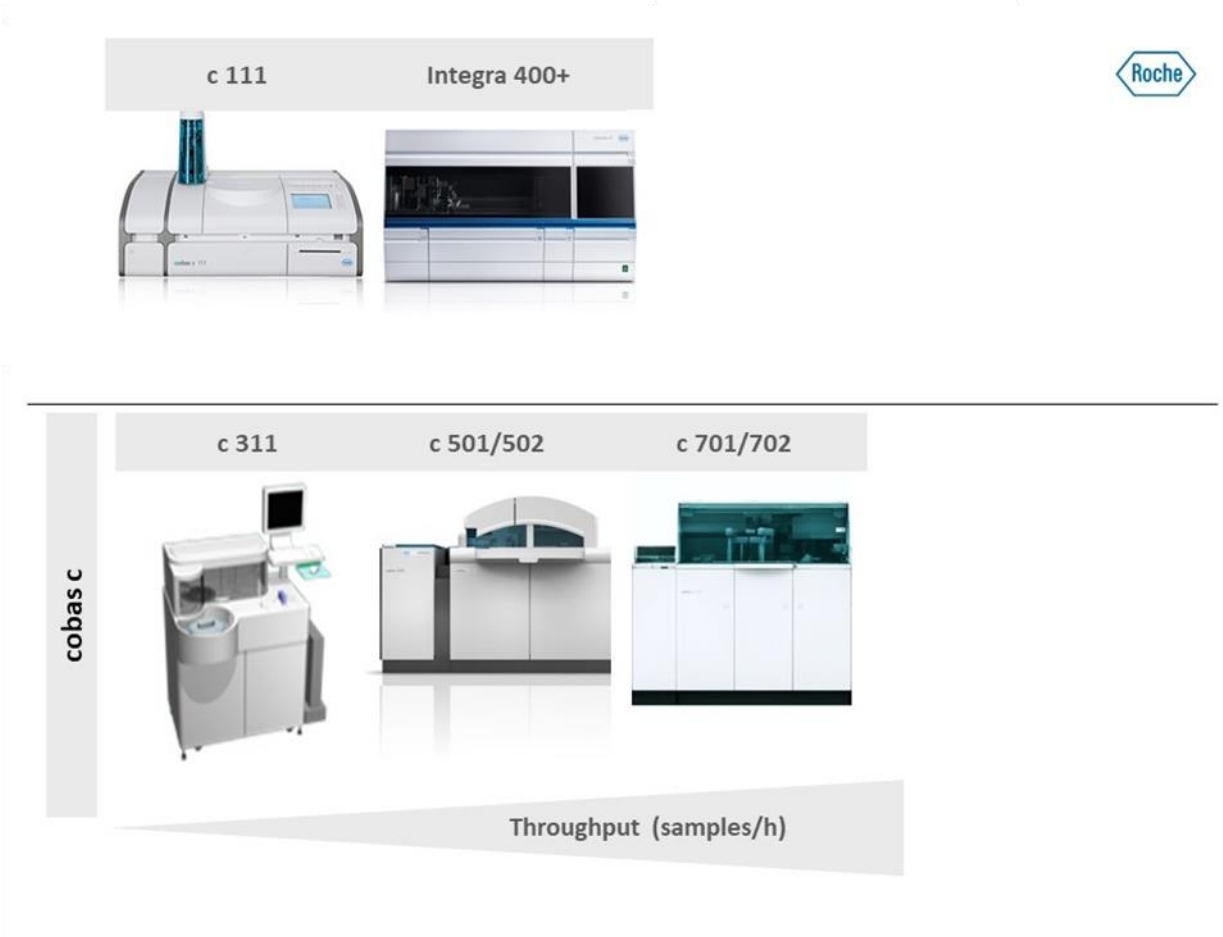

Figure 5. Examples for CC/DM analysers.

The operational conditions and risk management measures with respect to waste vary from one IVD module to the other and between different IVD assays. Risk management measures also vary from one laboratory / hospital to the other.

Hence, the operational conditions and waste handling for different instruments / assays are presented in the following section (9.3.1.1). In two further sections, the wastewater (9.3.1.2) and solid waste (9.3.1.3) situation in the UK and different laboratories / hospitals will be discussed.

9.3.1.1. Instruments and Assays

Table 8 gives an overview on the type of waste (solid / liquid) that is generated by the different types of instruments and assays. There are two types of waste fractions: waste from unused product or waste from empty cartridges including dead volumes and waste from the instruments after the assays have been performed.

Once used, empty reagent cartridges may still contain a dead volume of unused reagent which cannot be removed from the cartridge. All unused reagents in cartridges (e.g. from CC or DM assays) are disposed of as if they were hazardous solid waste (see waste scenario, Section 9.3.2.3). Note that most of these reagents are actually not classified as hazardous waste according to the waste regulations. However, instructions for waste disposal in the communication to customers were adapted to indicate to dispose of this waste ‘as if it was hazardous’. Corresponding handling of waste from cartridges was achieved by changes in the communication to customers. This was implemented by the EU sunset date on the 4th of January 2021.

Waste from the instruments after assays have been performed is disposed of as solid waste in the following cases. For some instruments, cuvettes that have been used still contain the reagents and are disposed of as such (e.g. Integra® 400+). All solid waste (e.g. cuvettes) is disposed of as hazardous solid waste (see waste scenario, Section 9.3.2.3).

However, for most instruments on which CC / DM or HIV assays are run, OPnEO and NPnEO are contained in concentrated liquid reagent waste from the instruments (high-concentrated waste: sample + reagents). This waste is either collected in a container (e.g. standalone instruments) or mixed with the diluted waste from rinsing steps (low-concentrated waste: rinsing water) and then directly released to wastewater (e.g. large laboratory installations with several cobas® modules). The instruments have two outlets for these two types of waste. The low-concentrated waste is estimated to contain less than 1% of the reagent volume and therefore, less than 1% of the overall amount of OPnEO / NPnEO used. Disposal of the concentrated waste depends on the applying local regulations on liquid waste as well as the setup of the laboratories (see Section 9.3.1.2). In some countries, treatment of waste for biohazard is required. Treating infectious waste for biohazard means the inactivation of possibly infectious germs (i.e. pathogens), e.g. by heating under pressure (autoclaving), incineration or chemical treatment, amongst other methods. In the UK, consents to discharge under the Water Industries Act 1991 (and other legislation, see Table 11) may require pre-treatment as a condition of the consent.

Table 8. Overview on type of waste that is generated during operation of instruments and assays and type of waste disposal. Instruments with significant release of OPnEO / NPnEO to wastewater are marked in bold.

Product Group	**Instruments**	**Solid waste**		**Liquid waste**	
		Type of waste	**Disposal***	**Type of waste**	**Disposal**
CC/DM	Integra® 400+	Reagents together with cuvettes and cartridges	solid hazardous waste	Low concentrated waste	release to wastewater
	cobas® 6000, module c501 / c502 **cobas® 8000, module c701 / c702** **cobas® c 311**	Empty and unused Cartridges	solid hazardous waste	High- and low-concentrated waste	release to wastewater
	cobas® c 111	Empty and unused Cartridges	solid hazardous waste	High-concentrated waste**	hazardous waste
HIV	**cobas® e 411**	Cartridges and infectious solid waste from samples with an average of 57% of total NPnEO	solid hazardous waste	High-concentrated waste with an average of 43% of total NPnEO**	release to wastewater
	cobas® 6000 / module e 601 **cobas® 8000 / module e 602**	Cartridges and infectious solid waste from samples with 57% of total NPnEO	solid hazardous waste	High-concentrated waste with an average of 43% of total NPnEO; Low concentrated waste	release to wastewater
RTD	**Benchmark**®	Dispensers	solid hazardous waste	Liquid waste	release to wastewater

*Most of the waste from unused product (in cartridges) is not classified as hazardous according to waste legislation. However, instructions in communication to customers state ‘disposal as if waste was hazardous’

** No low-concentrated waste since this small system has only one waste container where the entire liquid waste is collected.

Depending on the instrument, waste handling as recommended in the operator manuals or other communication to customers is different. Table 9 gives typical examples for waste handling instructions from operator manuals or other communication to customers for selected instruments and their reagents. For example, all solid waste from the Integra® 400+ instrument is disposed of as hazardous waste, whereas low-concentrated liquid waste (only containing very small amounts of OPnEO / NPnEO) is usually disposed via wastewater.

Table 9. Examples for waste handling instructions from operator manuals or other communication to customers for selected instruments

Product Group	**Instrument**	**Examples for waste handling from manual / other communication to customers**
CC/DM	Integra® 400+	'The system generates liquid and/or solid waste. This waste contains concentrated reaction solutions and is potentially biohazardous. Improper disposal may contaminate the environment. • Treat this waste as infectious waste. • Dispose of waste in accordance with the local regulations. The liquid waste from rinsing and cleaning operations is automatically removed from the analyzer. Waste system water is transferred either to an external container or to the laboratory waste system. Sample and reagent waste are removed with the cuvette. Used cuvettes are automatically dropped into the cuvette waste box. You have to remove the waste box and dispose of it, according to your local procedures for dealing with hazardous waste. ISE* waste is transferred directly to the cuvette waste box.'
CC/DM	cobas® 6000	'Contact with liquid waste may result in infection. All materials and mechanical components associated with the waste systems are potentially biohazardous. […] Waste must be treated in accordance with the relevant laws and regulations. Any substances contained in reagents, calibrators, and quality controls, which are legally regulated for environmental protection, must be disposed of according to the relevant water discharge facility regulations. For the legal regulations on water discharge, please contact the reagent supplier. Two kinds of liquid waste are discharged by the instrument: • Concentrated liquid waste that contains highly concentrated reaction solution. Treat this waste as infectious waste. Dispose of this waste according to the appropriate local regulations. • Dilute waste: A non-concentrated liquid waste diluted with rinsing water from cell wash or water from the incubator

Product Group	Instrument	Examples for waste handling from manual / other communication to customers
		bath. When using NaOH-D** for washing the reaction cells, alkaline concentration is 0.1 to 1.0 mmol/L in terms of sodium hydroxide equivalence. Dilute waste is discarded through tubes at the rear of the instrument. When disposing of any waste generated by the instrument, do so according to the relevant laws and local regulations. Liquid waste and replacement parts such as reaction cells and ISE* electrodes have to be treated as infectious medical waste.'
HIV	e411	'Infectious waste Contact with solid waste or waste solution may result in infection. All materials and mechanical components associated with waste systems are potentially biohazardous. […] Environmental harm The system generates liquid and/or solid waste. Liquid waste contains concentrated reaction solutions. Solid waste is potentially biohazardous. Improper disposal may contaminate the environment. • Treat liquid and solid waste as infectious waste. • Dispose of waste in accordance with the local laws and regulations. Any substances contained in reagents, calibrators, and controls must be disposed of according to the relevant water discharge facility regulations. • Contact the reagent manufacturer for information about the concentration of heavy metals and other toxic constituents of reagents, or for legal regulations on water discharge. […]'
CC DM	Assays	'Unused product and packaging waste must be sent to a licensed waste management company as the product contains a substance on REACH Annex XIV (substance of very high concern due to endocrine disrupting properties for the environment) at or above 0.1% w/w. <u>Waste treatment method</u>: Unused product: The unused product should not be allowed to enter drains, water courses or the soil. Do not contaminate ponds, waterways or ditches with chemical or used container. Collect the

Product Group	Instrument	Examples for waste handling from manual / other communication to customers
		unused product separately and send it to a licensed waste management company for disposal 'as if it was hazardous'. Used product: collect the used product separately and send to a licensed waste management company in those countries and for those instruments where technically and practically possible. Contaminated packaging: Empty remaining contents. Dispose of as unused product. Empty containers should be considered as packaging waste and should be taken to an approved waste handling site for disposal. Do not re-use empty containers.'
RTD	Assays	'Product: For customers in the European Economic Area and the UK: Contains SVHC: octyl/nonylphenol ethoxylates. For use as IVD only – cartridges / rests of product to be disposed of as if it was hazardous waste The product should not be allowed to enter drains, water courses or the soil. Do not contaminate ponds, waterways or ditches with chemical or used container. Send to a licensed waste management company. Contaminated packaging: Empty remaining contents. Dispose of as unused product. Empty containers should be taken to an approved waste handling site for recycling or disposal. Do not re-use empty containers.'

* ISE: Ion sensitive electrode for detection of Na, K and Cl
** NaOH-D: product name of the alkaline wash solution for cobas® c systems.

As can be seen in Table 8 and release estimates for the individual assays (see Annex 1 and 2), most releases to wastewater occur from CC / DM and HIV assays run on different cobas® instruments (see instruments marked in bold in Table 8). Therefore, in the following, more details are provided on operational conditions of these instruments and liquid waste volumes and concentrations of OPnEO / NPnEO in the liquid waste are estimated. For a discussion why further reduction of the release of OPnEO / NPnEO into wastewater is not technically and practically feasible please refer to Section 9.6.

Liquid waste volumes and concentrations of OPnEO / NPnEO

The table in Appendix 1 summarises estimated minimum and maximum volumes of high and low-concentrated liquid waste for each CC/DM as well as HIV and RTD modules from which release to wastewater occurs. Waste volumes are given per year based on typical hourly liquid waste volumes, operating hours per day and operating days per year. Based on the total number of modules of each type of module installed in the UK (see supporting document SD1_SEA_Nr_Instruments_RDL_Use3_CONFIDENTIAL to the SEA), a total liquid waste volume in the UK per year is estimated. Based on this estimation, a total of 1'600 – 9'150 m^3 high-

concentrated waste and a total of 18’200 – 97’700 m^3 low-concentrated waste is generated in the UK per year for CC/DM and HIV together. For RTD, [redacted] m^3 (100 – 1’000 m^3) of liquid waste are generated per year (see Table 10). Based on total amounts of OPnEO and NPnEO in CC / DM, HIV and RTD assays per year that are expected to be released to wastewater at the UK sunset date (see Annex 2), average concentrations of OPnEO and NPnEO are estimated (Table 11). This is based on the assumption that the affected assays are run on all installed modules. For CC / DM and HIV, high- and low-concentrated liquid waste fractions are combined (see Section 9.3.1.2). Therefore, OPnEO / NPnEO concentrations in high- and low-concentrated liquid waste (see Table 12) were estimated as follows:

- High-concentrated liquid waste (separate): 99% of OPnEO or NPnEO released from CC/DM or HIV assays to wastewater is assumed to be contained in the total high-concentrated liquid waste volume generated.

- Low-concentrated liquid waste (separate): 1% of OPnEO or NPnEO released from CC/DM or HIV assays to wastewater is assumed to be contained in the total low-concentrated liquid waste volume generated.

- Combined waste: 100% of OPnEO or NPnEO released from CC/DM or HIV assays to wastewater is assumed to be contained in the total liquid waste volume generated.

In each of these calculations, maximum and minimum concentrations were estimated as follows:

- Minimum concentrations: Amounts of OPnEO or NPnEO were assumed to be contained in the maximum estimated liquid waste volumes.

- Maximum concentrations: Amounts of OPnEO or NPnEO were assumed to be contained in the minimum estimated liquid waste volumes.

Estimated concentrations in liquid waste from CC/DM or HIV modules range from [redacted] mg/L OPnEO or NPnEO (0.001 – 50 mg/L) in high concentrated liquid waste, from [redacted] mg/L (0.00001 – 0.1 mg/L) in low concentrated liquid waste and from [redacted] mg/L (0.01 – 10 mg/L) in combined liquid waste. The actual OPnEO / NPnEO concentration in the high-/low-concentrated waste at any given time also depends on the working regime of the instrument (i.e. which tests were running on the instrument).

Table 10. Total amount of OPnEO and NPnEO used (worst-case for 2022) in CC/DM, RTD and HIV assays in the UK and estimated average ranges of concentrations of these substances in high- and low-concentrated liquid waste generated from the instruments.

Product Group	**Total amount released at the UK sunset date (kg/a) (worst-case)**	**Estimated average concentration (2022) (mg/L) or total waste volume (m^3)**					
		High-concentrated waste		**Low-concentrated waste**		**Combined (high- + low-concentrated)**	
		min	max	min	max	min	max
RTD*							
OPnEO (mg/L)	[redacted]	-	-	-	-	[redacted]	[redacted]
NPnEO (mg/L)	0	-	-	-	-		
Total waste volume from RTD (m^3)		-	-	-	-	[redacted]	[redacted]
CC/DM							
OPnEO (mg/L)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NPnEO (mg/L)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total waste volume from CC/DM (m^3)		1’141	7’135	11’587	69’705	12’728	76’840
HIV							
OPnEO (mg/L)	0	-	-	-	-	-	-
NPnEO (mg/L)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total waste volume from HIV (m^3)		450	1’998	6’611	27’998	7’060	29’996

*No low-concentrated waste since this system has only one waste container where the entire liquid waste is collected.

In a study on liquid waste from Roche IVD instruments [7], OPnEO was measured among other substances in the combined liquid waste (concentrated and diluted) from several **c**obas® 6000 / 8000 modules. Out of 8 measurements, 6 were below the limit of detection of 0.03 mg/L. In two samples OPnEO was detected at a concentration of 0.2 mg/L (0.00002% w/w) and 1.1 mg/L (0.0001% w/w), respectively. In the same study, OPnEO was also measured in aqueous liquid waste samples from Benchmark® instruments (RTD). Out of 5 measurements, 3 were below the limit of detection of 0.3 or 1 mg/L. In two samples OPnEO was detected at a concentration of 4 mg/L (0.0004% w/w) and 15 mg/L (0.0015% w/w), respectively. It has to be noted that only the aqueous liquid waste was analysed

for RTD samples. Some of the OPnEO may be present in the mineral oil phase of the liquid waste from Benchmark® instruments. Further measurements were available from December 2021 from effluent of the **c**obas® c6000/c8000 c701 where concentrations of NPnEO were below the limit of detection of 0.02 mg/L and those for OPnEO were below the limit of detection of 0.03 mg/L.

Only a few measurements are available due to limited access to samples from the laboratories / hospitals, as the sampling activity impacts the operation of the instrument. However, considering that the estimated values are average values and measured values represent waste samples during a specific moment of operating the instruments, measured values are in good agreement with the low estimated concentrations in liquid waste given in

Table 10, i.e. a range of [redacted] mg/L (0.1 – 10 mg/L) for OPnEO in combined waste for CC/DM and a range of [redacted] mg/L (5 – 30 mg/L) for RTD.

Amounts of OPnEO and NPnEO contained in the assays and the fractions that are released are known and available measurements are in good agreement with calculated values. Therefore, there would be no or limited added value of routine monitoring of OPnEO and NPnEO in liquid waste streams and such monitoring is not performed. In addition, as described above, high and low-concentrated liquid waste outlets are often directly connected to the sewer system. Therefore, routine sampling of liquid waste is not possible or would require complex procedures. Also, an analytical method has become available in 2019 (OPnEO) and end of 2021 (NPnEO) to measure OPnEO / NPnEO at low concentrations and measurements would have to be performed at an external laboratory. Routine monitoring would therefore be associated with high cost and logistic efforts.

9.3.1.2. Laboratory Wastewater Treatment Practices in the UK

In the UK laboratory wastewater is considered as trade effluent and a trade effluent consent is needed from the local water authority prior to commencing any trade effluent discharge. The elimination or diminution of a constituent of a trade effluent may be a requirement of consent. A permit for water discharge activities may also be required.

Table 11 (CC / DM and HIV) and Table 12 (RTD) give an overview of liquid waste collection and treatment in the UK. For CC / DM and HIV instruments, both concentrated and dilute liquid waste is usually released to wastewater. For RTD instruments, at some laboratories the mineral oil (i.e. organic) phase of the liquid waste (which may contain some of the OPnEO) is collected and treated (Table 12). However, this might not be the case for all laboratories. Pretreatment of liquid waste is not performed as a standard in UK laboratories, as there is no general legal requirement for this in the UK.

Table 11. Handling of liquid waste from the CC / HIV instruments in laboratories in the UK.

Approach to liquid waste collection	Approach to liquid waste treatment	Waste pre-treatment technologies installed	Legal background	Relevant legal text
For large automated systems the total liquid waste is released to wastewater. For smaller systems it is collected in on board containers on the instrument.	No treatment, release to wastewater.	No	Trade Effluent Consent and Permit for Water Discharge Activities	Pollution Prevention and Control Act 1999*) The Environmental Permitting Regs 2016**) Water Industry Act 1991***) Control of Pollution Act 1974****) Pollution Prevention and Control (Scotland) Regulations 2012*****) Sewerage (Scotland) Act 1968******)

*https://www.legislation.gov.uk/ukpga/1999/24/contents
**https://www.legislation.gov.uk/uksi/2016/1154/contents/made
***https://www.legislation.gov.uk/ukpga/1991/56/contents
****https://www.legislation.gov.uk/ukpga/1974/40/contents/scotland
*****https://www.legislation.gov.uk/ssi/2012/360/contents/made
******https://www.legislation.gov.uk/ukpga/1968/47/contents

Table 12. Handling of liquid waste from the RTD instruments in laboratories in the UK. For legal background and relevant legal text, please refer to.

Approach to liquid waste collection	Approach to liquid waste treatment	Waste pre-treatment technologies installed
Total liquid waste is always collected in onboard containers of the instrument.	Some customers take off the LCS (oil) layer, some dispose straight to sewage, others have the entire waste collected.	No

In addition to the general country information, information on specific laboratories for UK was also collected (see tables in Appendix 3 (CC/DM/HIV) and Appendix 4 (RTD)).

In conclusion, OPnEO- and NPnEO-containing liquid waste is usually directly released to wastewater. A removal of these compounds by pretreatment or collection and subsequent incineration of liquid waste from the instruments is not implemented as a standard in UK laboratories. Regarding pretreatment, it is unclear if any of the methods available on the market are efficiently removing OPnEO / NPnEO from liquid waste (for detailed discussion on pretreatment methods see Section 9.6). Therefore, it was assumed for the purpose of the present release estimation that the amount of

OPnEO and NPnEO in liquid waste from the instruments that is released to the sewer system or collected for treatment reaches the STP. Please refer to Section 9.6 for a discussion why the implementation of further risk management measures is not feasible for the downstream uses.

9.3.1.3. Laboratory Solid Waste Treatment Practices in the UK

The treatment of solid waste from the different assays (see Table 8) will depend on its classification as biohazardous waste. In case of solid waste from HIV assays, this is incinerated as potentially infectious (biohazardous) waste.

The amount of OPnEO and NPnEO being disposed of as solid waste from all products is estimated and accounted for separately. Release from waste disposal is estimated in waste scenarios for OPnEO and NPnEO. In the waste scenarios, it was assumed that all the OPnEO / NPnEO contained in solid waste is deposited in municipal landfills according to recommendations in the ECHA Guidance document (see description of approach for the waste scenarios in Section 9.3.2.3).

9.3.2. Environment

The current environmental exposure assessment was performed to support RDL's applications for authorisation to continue the use of the two groups of substances OPnEO and NPnEO at downstream user sites until complete substitution. Because of differences in their physical properties, toxicity towards aquatic organisms and available reference values of OPnEO and NPnEO, the two groups of substances are addressed in different exposure scenarios in the present CSR. However, the scope and type of the environmental assessment as well as the general approach followed to estimate the total releases and environmental exposure presented in the following apply to both OPnEO and NPnEO. Therefore, the present introduction to the environmental assessment is described in one common part for OPnEO and NPnEO.

9.3.2.1. Scope and Type of Assessment

In a first step, the initial releases of OPnEO / NPnEO in the UK were estimated for the developed exposure scenarios based on the figures given in the AfA submitted by RDG in the EU, and subsequently scaled down to the UK market using the percentage of the total number of instruments (EEA and the UK) installed in the UK (see sections 9.2.2.1 and 9.2.3.1 for details). The data were collected in 2016/2017 on relevant uses at the downstream users' sites i.e. laboratories / hospitals, and blood banks across the EEA (including the UK at the time) considering risk management measures (RMMs) that were planned to be in place at the EU sunset date.

For downstream user sites, the main releases of OPnEO / NPnEO occur via the release to wastewater from the sites to STP. There are no direct releases to soil from downstream users' sites. Direct releases to the air from downstream users' sites are not expected due to the very low vapor pressure of OPnEO / NPnEO (≤7.5E-03 mm Hg, for details see supplementary document SD2a to this CSR). However, releases to soil and air are considered when addressing the removal processes taking place in the STP and the application of sludge to agricultural soil.

In a second step, the removal processes and setup for a standard STP assumed for downstream user sites were described and assessed in order to be reflected in the model used for the prediction of the exposure concentrations in the relevant environmental compartments after STP. Details on the approach followed for the estimation of the initial releases and the description of the removal processes taking place in a standard STP assumed for downstream user sites are provided in Section 9.3.2.2.

In a third step, exposure estimation to all relevant environmental compartments as listed in Table 13, were calculated with the 'Multifate' model [10] which reflects the degradation mechanism specific to OPnEO / NPnEO that cannot be described with the standard EUSES model [11].

Table 13. Type of risk characterisation required for the environment.

Protection target	Exposure estimation	Type of risk characterisation
Freshwater	Quantitative	Qualitative – risk minimisation
Sediment (freshwater)	Quantitative	Qualitative – risk minimisation
Marine water	Quantitative	Qualitative – risk minimisation
Sediment (marine water)	Quantitative	Qualitative – risk minimisation
Sewage treatment plant	Quantitative	Qualitative – risk minimisation
Air	Quantitative	Qualitative – risk minimisation
Agricultural soil	Quantitative	Qualitative – risk minimisation
Soil porewater / groundwater	Quantitative	Qualitative – risk minimisation

In agreement with the RAC statement from December 2017 [1], the PECs estimated with the 'Multifate' model for OPnEO / NPnEO and its expected biodegradation products including OP / NP were all converted to equivalents of OP / NP (based on molecular weight) as it should be assumed that all OPnEO / NPnEO released to the environment ultimately ends up as OP / NP. More details on the model are provided in Section 9.3.2.5.1.

Releases to fresh and marine waters from STP and partition to sediments (fresh waters and marine) are considered for the assessment. In addition, releases to soil and air from STP are considered when addressing the removal processes taking place in the STP and for application of sludge to agricultural soil. In the UK, application of sludge to agricultural soil is regulated under 'The Sludge (Use in Agriculture) Regulations 1989' [21]. On average appr. 80% of total sewage sludge are used in agriculture, the remaining appr. 20% are mainly incinerated or disposed of otherwise [22]. As in one region 100% of sludge may be applied on soil, for the model calculations in this CSR it was assumed that 100% of sewage sludge is applied on soil as a worst-case. This applies to the regional and to the local model for the wide-dispersive uses as covered in this CSR. Based on the calculated concentrations of OP / $NP_{equiv.}$ in soil, porewater concentrations and hence, according to the guidance document [19], groundwater concentrations were calculated according to the guidance document [19]. However, it can be assumed that, based on the high logKoc of the substances (for physico-chemical data see SD2a_CSR_Model_description_partI_general_RDL_Use3; Tables 1 and 2), leaching will play a minor role and contamination of groundwater / surface water via sewage sludge disposed on soil will be minimal. The exposure to predators was not addressed in this CSR because OP / NP is not expected to bioaccumulate ([1][9]).

To confirm that the 'Multifate' model used for this assessment is adequate, the calculated PECs in surface water (local) were compared with data obtained from monitoring campaigns performed at the EU production site in Penzberg. More details on the monitoring campaigns are provided in Section 9.3.2.5.2.

In the current exposure assessment, the activities in relation with Use 3 are addressed in Section 9. A combined estimation of the local release per site and combined estimation of regional release is not required as there are no releases from production sites (no production of Roche's IVD assays in the UK).

Finally, although a direct comparison of the combined local PECs with a reference value is not applicable to non-threshold endpoints, the combined calculated PECs per site were compared with available reference values such as EQS values from the Water Framework Directive (Standards and Classification) Directions (England and Wales) 2015 [13] as supporting information (see Section 9.3.2.6 for more details).

9.3.2.2. Specific approach for Laboratories / hospitals

The main downstream user of the IVD assays are laboratories / hospitals as described in Section 9.3.1. The releases of OPnEO / NPnEO from the laboratories / hospitals occur mainly via the introduction of the liquid waste streams from the IVD modules (instruments). The wastewater containing OPnEO / NPnEO from laboratories / hospitals is collected in a central public sewer system and ultimately enter the local municipal STPs. A high number of UK customers, i.e. laboratories / hospitals purchases IVD assays from RDL (>1'000 instruments installed in the UK (see detailed figures in the SEA)). Therefore, a wide-dispersive use based on the standard risk assessment under REACH with specific adaptations to the situation in UK was assumed for the purpose of the exposure assessment (for details see paragraph below 'wide-dispersive approach').

As described in Section 9.3.1, from some instruments waste of used reagents and test samples is collected at laboratories / hospitals. In addition, for all assays, waste of unused product is collected. This is assessed in a separate waste scenario (see Section 9.3.2.3).

There is no direct release to the soil or the air at laboratories / hospitals.

Wide-dispersive approach

The total annual usage for all laboratories / hospitals in the UK was calculated as the sum of the total annual amounts of OPnEO / NPnEO present in the imported assays.

This estimation was based on data collected for 2016-2017 given in the AfA submitted by RDG in the EU and scaled down to the UK for all relevant assays and was extrapolated to the UK sunset date in 2022 considering the evolution of the amounts related to the expected sales development or predictions of production volumes (see sections 9.2.2.1 and 9.2.3.1 for details).

Considering a wide-dispersive use for the laboratories / hospitals implies that only a fraction of the total annual usage for all laboratories / hospitals is used in a standard town and that the corresponding releases are collected in a central public sewer system and then treated in a municipal STP.

For the purpose of the assessment, the exposure of the regional environment was assumed to take place over the whole area of the UK (250'000 km2), having a population of about 67 million inhabitants. This is an adaptation of the EU standard region as foreseen in the guidance on information requirements and chemical safety assessment, chapter R.16 [17] to the settings applicable in the UK. Therefore, regional exposure was calculated taking into account 100% of releases of Use 3 (EU standard region: 10%). Further, the fraction of the regional amount used locally was adapted to 1'000 (EU standard fraction: 2'000). This adaptation was necessary because data on average size laboratories indicated that the total used amount of OPnEO / NPnEO in UK is probably distributed

over fewer locations compared to the standard EU scenario. Therefore, for the purpose of the assessment, the daily wide-dispersive use was estimated per site starting from the maximum annual usage for all laboratories / hospitals in the UK dividing it by:

- 1: Fraction of the total amount at UK level used in the region,
- 1’000: Fraction of the regional amount used in the standard town of 67’000 inhabitants (versus 67’000’000 inhabitants in the region), based on total annual usage compared to the annual usage in an average sized laboratory,
- 255 or 360 (day/a): number of operating days in a year defined per product group and multiplying it by a safety factor of 4 to consider geographical or temporal variations in the use and releases as recommended in ECHA Guidance R16 [12].

Based on these factors, the fraction of the total amount used per site per year is 0.004 (4 / (1×1000)).

The daily wide-dispersive use amount per assay $Q_{daily,\ assay}$ (kg/day) was then calculated as follows:

$Q_{daily,\ assay}$ (kg/day) = total annual usage for all laboratories / hospitals in the UK (kg/a) for a given assay × 4 / (1×1’000×255 or 360 days/a) as determined in the ECHA Guidance R16 [12].

The total daily wide-dispersive used amount $Q_{daily,\ stite}$ (kg/day) per site was then calculated as follows:

$Q_{daily,\ site}$ (kg/day)= $\sum Q_{daily,\ assay}$

As discussed previously, depending on the assay and the instrument, unused product as well as parts of used assays / reagents are collected and disposed of as waste. The release to STP was therefore set to 84% of total amount for OPnEO and 47% of total amount for NPnEO. These fractions were determined based on specific information per product group (see Section 9.3.1.1) including risk management measures already implemented. In particular, this includes disposal of unused product as waste based on updated instructions for disposal in communication to customers. Further minimisation of releases to STP from the laboratories / hospitals through risk management measures are not technically and practically feasible as discussed in Section 9.6.

Details on the calculation of the total daily wide-dispersive used amount per site and at the level of the concerned assays can be found in supporting documents SD4a_CSR_Usage_Releases_OPnEO_RDL_Use3_CONFIDENTIAL and SD4b_CSR_Usage_Releases_NPnEO_RDL_Use3_CONFIDENTIAL.

Validity of the wide-dispersive approach

To verify that the assumption of a wide-dispersive use was justified, for the EU dossier additional information was collected on the use of IVD assays containing OPnEO / NPnEO for an average size and a big laboratory / hospital and a blood bank to reflect the variability in the compositions of the laboratories / hospitals / blood banks. Typically, data on the total number of tests run per year, the total amount of OPnEO or NPnEO per test etc. were collected per type of assay or measured parameter. In general, it is assumed that the collected information for an ‘average’ and a ‘big’ laboratory is also applicable to UK laboratories. This assumption was confirmed by comparing the total annual usage based on the EU data scaled down to the UK with the total annual usage estimated based on total number of installed modules in the UK (see Appendix 1) and average/maximum usage per module per year (see SD3a and SD3b). As a result, both approaches gave similar total annual

usage and therefore, the data for ‘average’ and ‘big’ laboratories was taken from the EU dossier, with only minor adjustments (e.g. number of operating days). For one assay (RTD), there was specific information for UK laboratories available, which was considered in the calculations (higher number of assays per year per laboratory). A summary of the collected data is reported in supporting documents SD3a_CSR_Data_collected_OPnEO_RDL_Use3_CONFIDENTIAL and SD3b_CSR_Data_collected_NPnEO_RDL_Use3_CONFIDENTIAL.

From this data, the daily use amount (kg/day) was derived for OPnEO and NPnEO for each category of assay based on the number of tests performed in an average size and a big laboratory / hospital in the UK.

As a worst-case it was assumed that all types of assays are being run in parallel by the average size and the big laboratory / hospital. Therefore, the total daily local use amount for an average size / big laboratory / hospital (kg/day) was calculated as the sum of the average / maximum daily use amount of OPnEO / NPnEO derived for each type of assay for the relevant exposure scenarios.

The calculated total daily local use amount for an average size laboratory / hospital (kg/day) was then directly compared with the daily local wide-dispersive use amount calculated following the adapted wide-dispersive approach.

In case of OPnEO, both approaches were in good agreement. However, in case of NPnEO further adaptations were needed. Data for an average size laboratory / hospital indicated higher use amounts compared to the adapted wide-dispersive scenario, i.e. the total used amount of NPnEO is probably distributed over fewer locations in UK compared to the assumptions in the adapted wide-dispersive scenario. NPnEO is mainly used in form of HIV assays. Therefore, the fraction of the total amount used per site for HIV was increased by a factor of 7, resulting in a fraction of 0.025 (instead of 0.004 for OPnEO) used at local scale for NPnEO (over all assays). After this adaptation for NPnEO, both approaches were in good agreement and the total wide-dispersive daily site use was selected for the purpose of the environmental exposure assessment (see details in supporting documents SD4a_CSR_Usage_Releases_OPnEO_RDL_Use3_CONFIDENTIAL and SD4b_CSR_Usage_Releases_NPnEO_RDL_Use3_CONFIDENTIAL).

Using this value, the release to STP was calculated based on the percentage of release for each assay taking into account the percentage of used and unused product disposed of as waste (see details in supporting documents SD4a_CSR_Usage_Releases_OPnEO_RDL_Use3_CONFIDENTIAL and SD4b_CSR_Usage_Releases_NPnEO_RDL_Use3_CONFIDENTIAL).

To assess maximum local release, a calculation was performed using the total daily local use amount for the big laboratory / hospital and a big blood bank. Calculations and results for a big laboratory and blood bank are further discussed in Sections 9.4.1.2.4 and 9.5.1.2.4.

In addition to the calculated usage and release to STP, information on the specific parameters of the STP as well as the removal steps occurring in the STP are required as input of the ‘Multifate’ model used to estimate the releases after STP and PECs in the relevant environmental compartments.

For wide-dispersive uses, releases to wastewater are assumed to be collected in a central public sewer system and to be then treated by a standard biological STP to which the 67’000 inhabitants of a standard town are connected (ECHA Guidance R16 [12]).

The characteristics of the standard biological STP as described in ECHA Guidance R16 [12] which were also used in the 'Multifate' model are further described in the model description (see supporting document SD2b_CSR_Model_description_partII_RDL_Use3). In case of OPnEO. for the big laboratory / hospital the local scenario was adapted to specific conditions of the location of the big laboratory (see section 9.4.1.2.4 and SD2b_CSR_Model_description_partII_RDL_Use3).

To allow a realistic estimation of the total releases of OPnEO / NPnEO after the standard biological STP and the corresponding exposure estimation to all relevant environmental compartments, the typical removal processes of OPnEO / NPnEO taking place in the REACH standard biological STP were implemented in the 'Multifate' model using the parameters provided in supporting document SD2b_CSR_Model_description_partII_RDL_Use3. The indirect releases from the STP to air and to soil via sewage sludge application were considered for the exposure assessment at the local (air and sludge) and regional (sludge) scale.

9.3.2.3. Waste Scenario

For assessing the exposure from waste, the approach as described in the ECHA guidance Chapter R18 (Version 2.1, ECHA, 2012 [19]) was followed. The environmental exposure concentrations for the waste life stage are reported for each exposure scenario.

Defining the waste streams

The life cycle stage of OPnEO / NPnEO addressed in this assessment include the use in IVD assays at laboratories / hospitals / blood banks. At this stage, waste is produced for which risks have to be assessed. In a first step, the fraction of OPnEO / NPnEO being disposed of as waste has to be defined. This is the percentage of the used volume of each substance entering a particular waste stream or waste treatment process.

The following different types of solid waste are created during/after use in IVD assays:

- Waste in cartridges / containers (unused product / reagents as manufactured) at laboratories / hospitals / blood banks
- Waste from running the assays (collected as solid waste, reagent waste together with cuvettes from the measurements and treated as infectious waste) for some assays / instruments at laboratories / hospitals

For a more detailed overview please refer to Table 8.

To calculate these overall amounts, the amount being disposed of as waste was calculated for each individual assay for CC, DM and HIV taking the following into account:

- The percentage remaining as dead volume in the cartridges.
- The amount being disposed of from assays run on Integra® 400+ or cobas® c111 with complete disposal as waste (CC / DM).
- The percentage going to infectious solid waste from samples (HIV).

The total maximum amounts of OPnEO / NPnEO being disposed of as waste (assuming that all substitutions are delayed) were identified as follows: OPnEO: 7.88 kg/a, NPnEO: 0.206 kg/a.

For the waste scenario, the following conservative assumptions were made according to the recommendations in the ECHA guidance document [19]:

- All of the OPnEO / NPnEO contained in solid waste ends up in municipal waste (even though the communication to customers recommends treating waste of unused product 'as if it was hazardous' and hence, a large part of the solid waste may end up in hazardous waste landfills / treatment facilities).

- All of the OPnEO / NPnEO contained in solid waste is deposited in municipal landfills (even though only 23% of all waste was landfilled in 2018 in the UK [23]).

As stated above, some of the waste may be incinerated which is not accounted for in the waste scenario. The incineration temperature for hazardous waste must be at least 1'100 °C and at least 800 °C for municipal waste [25][24]. As OPnEO will be completely destroyed at an incineration temperature of 400 °C [20], it can be assumed that after incineration of waste containing OPnEO either as hazardous or municipal waste, no OPnEO will be released to the environment. In analogy, the same can be assumed for NPnEO. Therefore, the above assumptions represent a worst-case regarding the release to the environment from waste.

General methodology

Local release assessment

The methodology to be followed to assess emissions and risks from waste is given in the ECHA guidance R18 [19]. The following parameters have to be estimated:

- Fraction of total amount per use being disposed of as solid waste and entering into a specific (or generic) waste treatment process (f_{waste}, expressed in % of amount per use).

- The maximum processed daily amount of OPnEO / NPnEO contained in wastes at one waste treatment site per day ($Q_{max, local}$, expressed in kg/day).

- The release factors to the environmental compartments air, water and soil (RF_{air}, RF_{water} and RF_{soil}).

Based on the above parameters, the local daily release (kg/day) ($E_{local, env}$) per compartment can be calculated [25]. This information is then entered into the 'Multifate' model to obtain the local predicted environmental concentrations (C_{local}) for the different compartments.

The release rates are calculated using the following equation:

$$E_{local\ env} = Q_{max,local} * RF_{env}$$

Q max is calculated as follows:

$$Q_{max,local} = Q\ (t/a) * f_{waste} * 1000 * DF / T_{emission}$$

Where:

Q = total volume of OPnEO / NPnEO per use (t/a)

f_{waste} = fraction of OPnEO / NPnEO per use becoming waste and entering a waste stream

DF = factor characterising the dispersiveness of use and corresponding treatment

$T_{emission}$ = days of operation of a waste treatment installation (d/y) =365 days

The release of OPnEO / NPnEO to the environment during the waste stage depends on the number and distribution of installations where the treatment takes place. As a wide-dispersive use is assumed for the assessed use at laboratories / hospitals / blood banks, a DF of 0.001 is assumed related to the total UK amount [19]. However, based on the assumption that the municipal sewage treatment structure in the UK is more dispersive than the municipal waste treatment structure, a concentration factor should be considered which is derived from the number of waste treatment installations compared to the number of municipal sewage treatment installations. For landfill the concentration factor is reported to be 2.71 (i.e., where 1 wastewater treatment plant is assumed per 8'300 inhabitant equivalents, there is on average only 1 landfill site per 22'500 inhabitant equivalents in the UK [25]). This concentration factor, for wide-dispersive uses, should be multiplied with the DF. Hence, an adjusted DF of 0.000369 was applied for the laboratories / hospitals / blood banks use in accordance with [19].

Regional release assessment

The methodology to be followed to assess emissions and risks from waste for regional assessment is given in the ECHA guidance R18 [19]. The following parameters have to be estimated:

- Fraction of total amount per use being disposed of as solid waste and entering into a specific (or generic) waste treatment process (f_{waste}, expressed in% of amount per use)
- The annual amount of OPnEO / NPnEO contained in wastes treated in the region (Qmax, regional, expressed in [t/y])
- The release factors to the environmental compartments air, water and soil (RF_{air}, RF_{water} and RF_{soil}).

Based on the above parameters, the regional daily release (kg/day) ($E_{regional, env}$) per compartment can be calculated [25]. This information is then entered into the 'Multifate' model to obtain the regional predicted environmental concentrations ($C_{regional}$) for the different compartments.

The release rates are calculated using the following equation:

$$E_{regional\ env}\ [t/y] = Q_{max,regional}\ [t/y] * RF_{env}$$

Q max is calculated as follows:

$$Q_{max,regional} = Q\ (t/a) * f_{waste} * 0.1\ (dispersive\ uses)$$

Where:

Q = total volume of OPnEO / NPnEO per use (t/a)

f_{waste} = fraction of OPnEO / NPnEO per use becoming waste and entering a waste stream

0.1 represents the default fraction of the total amount used in the region for wide-dispersive uses according to [19].

Derivation of release factors to soil, air and water

The release factor to air from a landfill according to Table R.18- 4 of the guidance document [19] was set to zero since releases to air of non-VOC is regarded as negligible. The release factor to soil was set to 0.0016 according to the guidance document [19] since it cannot be excluded that OPnEO / NPnEO could (laterally) pass through the landfill body and the mineral layers of the landfill. This is however unlikely, as their degradation products OP and NP, due to their high log Koc, would likely adsorb to the solid phase and organic matter and hence, would be more likely to remain in the landfill body (either included into the matrix or adsorbed to organic waste particles or liner materials) than to leach [19]. It must be noted though, that degradation of OPnEO / NPnEO to OP / NP was not taken into account in the landfill scenario for simplification. The main source of OPnEO / NPnEO will enter the aquatic compartment through the leachate produced at the landfill site. The default release factor to water of 0.032 [19] is considered for the assessment as no measured leachate data is available. The number of operating days of a landfill is set at 365 days/a.

Summary of release factors for each scenario (local and regional):

RF to air = 0

RF to soil = 0.0016

RF to water = 0.032

Emissions to environmental compartments

The local and regional releases to wastewater calculated in the way depicted above were used as input to the local and regional modules of the model 'Multifate' as described in Section 9.3.2.5.1, using standard parameters for STP, rivers and dilution in the environment as described for the wide-dispersive release from average laboratories. For the big laboratory / hospital the local scenario was adapted to specific conditions of the location of the big laboratory (see SD2b_CSR_Model_description_partII_RDL_Use3).

The calculated local PECs from waste were added up with the local PECs from the use itself since one local compartment could receive the releases from both the use itself and the treatment of the waste from the use, i.e. the release from landfill (see Sections 10.1.2.1.2 and 10.2.2.1.2). Furthermore, the regional PECs from waste were added up to the regional PECs from the use itself to receive total regional PECs (see Sections 10.1.2.1.1.2 and 10.2.2.1.1.2). In addition, local PECs were then added to regional PECs to receive total local exposure due to wide-dispersive uses (see Section 10.1.2.1.2 and 10.2.2.1.2).

For the calculation of soil concentrations, the standard areas for the local scenario (circular area with a radius of 1000 m) and a region (250'000 km^2, total area of the UK) were assumed according to the guidance document [12]. Furthermore, a mixing depth for agricultural soil of 0.2 m and a bulk density of wet soil of 1700 kg/m^3 were assumed [12] to calculate local and regional soil concentrations due to waste. Degradation was not assumed to occur and the OPnEO / NPnEO concentrations were converted to OP / $NP_{equiv.}$ Due to the substance properties (high log Koc values), the calculated concentrations likely represent overestimations.

9.3.2.4. Approach for the Regional Exposure

For the purpose of the assessment, the exposure of the regional environment was assumed to take place over the whole area of the UK (250'000 km^2), having a population of about 67 million inhabitants. This is an adaptation of the standard region as foreseen in the guidance on information

requirements and chemical safety assessment, chapter R.16 [12] to the settings applicable in the UK. Therefore, regional exposure was calculated taking into account 100% of releases of Use 3. The regional exposure of OPnEO / NPnEO and their degradations products was also assumed to occur continuously over the year in agreement with [12] in this CSR.

9.3.2.5. Environmental Exposure Modelling and Monitoring

9.3.2.5.1. Environmental Exposure Modelling

In the classical approach, initial release to STP is typically calculated from the total used amount considering the standard release factors to wastewater, and thus to STP, for a given scenario. Instead, in this assessment, the maximum daily release to wastewater based on the collected data was used as input of the model used to estimate the PECs in the relevant environmental compartments.

The model 'Multifate' [10] was developed in the framework of a scientific research project. The latter had the overall goal to assess the relevance of endocrine disruptors to humans, animals and ecosystems[2]. An application of the model to various substances exhibiting endocrine disrupting potential has been published [10]. 'Multifate' is a model based on fugacity and hence calculates mass flows to and from all environmental compartments (air, groundwater, soil, surface water and sediment) based on phase equilibria. In contrast to EUSES [11], 'Multifate' incorporates specific degradation products. The fate of these degradation products is also calculated making 'Multifate' a combined multi-compartment and multi-substance model. 'Multifate' was developed for nonylphenol ethoxylates (NPnEO) and its degradation products nonylphenoldiethoxylate (NP2EO), 4-nonylphenoxyethoxyacetic acid (NP2EC), nonylphenolmonoethoxylate (NP1EO), 4-nonylphenoxyacetic acid (NP1EC) and 4-nonylphenol (NP). The degradation mechanism used in 'Multifate' is shown in Figure 1 in supporting document SD2a_CSR_Model_description_partI_general_RDL_Use3. The same degradation mechanism was assumed for OPnEO based on the general degradation mechanism that holds for all alkylphenol polyethoxylates according to [16] and [1].

9.3.2.5.2. Monitoring

Laboratories / hospitals

No monitoring campaign was conducted at a laboratory / hospital or an associated STP since the exact source of OPnEO and NPnEO in such effluents would be difficult to trace. Indeed, these substances could also be present in a range of other uses, e.g. in textiles (EU REACH restriction for NPnEO in textiles only came into effect 2021), paints, various products for consumer and professional uses (e.g. cleaning products, lubricants, detergents, biocidal products) [9]. Hence, the concentrations in effluents were estimated using the 'Multifate' model and modelled values are compared with data available from monitoring in different surface waters across Europe.

However, monitoring data from the EU production site in Penzberg were used to verify the assumptions of the 'Multifate' model. The comparison of monitoring data with the modelled data confirmed that the assumptions used in the model 'Multifate' were very conservative (e.g., 100% of OPnEO released to wastewater; no complete mineralization), as the modelled concentrations were always by a factor of 30 to 440 higher compared to the measured data. Detailed data of this comparison are given in the CSR of Use 4 of the EU dossier in section 9.4.5. 'Results of the

[2]Research project on endocrine disruptors: http://www.snf.ch/en/researchinFocus/nrp/nrp50-endocrine-disruptors-relevance-to-humans-animals-and-ecosystems/Pages/default.aspx

Monitoring Data and Validation of the 'Multifate' Model'[3]. Also, measured concentrations in liquid waste from IVD instruments are discussed in Section 9.3.1.1.

9.3.2.6. Comparison with Reference and Background Values

Selected EQS values or PNEC from several sources are given in Table 14. The values were selected for comparison in the assessment since they represent the official EQS values (e.g. from the Water Environment (Water Framework Directive) (England and Wales) Regulations 2015 [13]), or they are newly derived values that are lower (e.g. [14]) than the presently valid official values.

Table 14. Selected EQS and PNEC values from several sources. AA-EQS: Annual average environmental quality standard; MAC-EQS: Maximum allowable concentration environmental quality standard.

Value type	Value specific for	Value (µg/L)	Substance	Source
AA-EQS	Marine & limnic systems	0.043*	4-nonylphenol, branched and linear	[14]
MAC-EQS	Marine & limnic systems	3.8*	4-nonylphenol, branched and linear	[14]
AA-EQS	Inland surface waters / Other surface waters	0.3**	4-nonylphenol, branched and linear	[13]
MAC-EQS	Inland surface waters / Other surface waters	2**	4-nonylphenol, branched and linear	[13]
PNEC	Pelagic marine and freshwater	0.39***	Nonylphenol	[9]
AA-EQS	Inland surface waters****	0.1	Octylphenol, CAS 140-66-9	[13]
AA-EQS	Other surface waters	0.01	Octylphenol, CAS 140-66-9	[13]
MAC-EQS	Water	not applicable*****	Octylphenol, CAS 140-66-9	[13]
PNEC	Freshwater	0.034******	4-t-Octylphenol, CAS 140-66-9	******

* before update (i.e. 2011): AA-EQS: 13 ng/L and MAC-EQS: 3.27 µg/L; according to the Swiss Ecotox Centre, these data were provided to the EU and will likely be incorporated into new WFD values; values determined by specific SSD approach

** value is intended to be revised

*** value determined using an AF=10 on the lowest valid chronic pelagic NOEC which is the marine mysid Americamysis bahia (formally Mysidopsis bahia) NOEC (endpoint: reduced growth measured as length) of 3.9 µg $_{NP}$/l

**** Inland surface waters encompass rivers and lakes and related artificial or heavily modified water bodies

***** According to the water framework directive [13]: "Where the MAC-EQS are marked as "not applicable", the AA-EQS values are considered protective against short-term pollution peaks in continuous discharges since they

[3] Link to CSR of Use 4: https://echa.europa.eu/documents/10162/0775aa16-4c55-77b6-0d94-013c5ffae586

are significantly lower than the values derived on the basis of acute toxicity".

****** PNEC value as determined in the hazard assessment of this CSR ("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, Patricia Janz, Christiane Brandt) derived from a NOEC of 0.34 µg/L (measured concentration) for the total number of embryos in a weight-of evidence approach using data from OECD guideline 242 validation study / range-finding test. See supporting document to the CSR 'SD1_CSR_Hazard_assessment_OPnEO_RDL_Use3'.

Background values

Available and current levels of NP and OP in a range of surface waters and in marine water are shown in Table 15. There is one measurement available for the UK. To give a broader idea of measured concentrations in the environment, also data from EU countries are included here. These values are used for comparison of the modelled and measured data (see Sections 10.1.2.1.3 and 10.2.2.1.3 risk assessment).

Table 15. Concentrations of NP and OP measured in surface and marine water.

Substance	Value (µg/L)	Source	Link	Remark
NP	0.085	[9] (Table 34, p. 192)		Median of a range of NP data in a range of different countries
NP	0.05	[9] (p. 189)		Median of a range of NP data in marine water
NP	0.105±0.038	IKSR database	https://iksr.bafg.de/iksr/	Germany, Koblenz, Rhine; average 2015
NP	0.092±0.029	IKSR database	https://iksr.bafg.de/iksr/	Germany, Koblenz, Rhine; average 2016
NP	measured concentrations of NP in surface waters mostly below the detection limit; risk quotients <1 using the WFD - EQS	Maßnahmen zur Verminderung des Eintrages von Mikroschadstoffen in die Gewässer, Umweltbundesamt 2015	https://www.umweltbundesamt.de/publikationen/massnahmen-zur-verminderung-des-eintrages-von-0	Germany
NP	Bosnia and Herzegovina <0.0500 Belgium <0.0431 Spain <0.5200	EIONET database	https://forum.eionet.europa.eu/nrc-eionet-freshwater/library/hazardous-substances-report/country-review-hazardous-substances-water-etc-icm-report-2014/hs_data_etc-	River data from 11 countries for 2002-2011. Reported concentrations were below EQS, except for 10% of

Substance	Value (µg/L)	Source	Link	Remark
	France <0.1500 Italy <0.1000 Lithuania <0.1100 Luxembourg <0.0617 Romania <0.0762 Slovenia <0.0260 Slovakia <0.0667		icm_technical_report_2014_for_country_review	samples from Spain that were above EQS (0.3 µg/L).
NP/OP	NP and OP exceeded the EQS in five or less (of ten) river basin districts in Germany	[15]	www.mdpi.com/2073-4441/8/6/217/pdf	Germany
OP	0.022±0.08	IKSR database	https://iksr.bafg.de/iksr/	Germany, Koblenz, Rhine; average 2015
OP	0.021±0.08	IKSR database	https://iksr.bafg.de/iksr/	Germany, Koblenz, Rhine; average 2016
OP	France: 0.71 **UK: 0.037** Slovakia: <1.00	EIONET database	https://forum.eionet.europa.eu/nrc-eionet-freshwater/library/hazardous-substances-report/country-review-hazardous-substances-water-etc-icm-report-2014/hs_data_etc-icm_technical_report_2014_for_country_review	Maximum concentrations (groundwater; µg/l), 2002-2011

9.3.3. Man via Environment

Risks to human health via the environment do not need to be assessed in the CSR included in an application for authorisation for OPnEO and NPnEO as they were listed on UK REACH Authorisation List (Annex 14) only on the basis of their endocrine disrupting properties for the environment (EU REACH Article 62(4)).

9.3.4. Workers

Risks to human health do not need to be assessed in the CSR included in an application for authorisation for OPnEO and NPnEO as they were listed on UK REACH Authorisation List (Annex

14) only on the basis of their endocrine disrupting properties for the environment (EU REACH Article 62(4)).

9.3.5. Consumers

Risks to human health do not need to be assessed in the CSR included in an application for authorisation for OPnEO and NPnEO as they were listed on UK REACH Authorisation List (Annex 14) only on the basis of their endocrine disrupting properties for the environment (EU REACH Article 62(4)).

9.4. Exposure Assessment for OPnEO

- ⇨ Considering the RMMs in place, the total release of OPnEO to wastewater is **33.33 kg/a** at the downstream sites for the use applied for **at the UK sunset date**.
- ⇨ The **maximum annual release of OPnEO to wastewater** potentially reached over the review period at the end of 2027, assuming that all substitutions are delayed (worst-case), is **40.77 kg/a** at the downstream sites.

9.4.1. Exposure Scenario 1: PW1 – OPnEO - Use in IVD assays for laboratories / hospitals

Sector of use: SU20 – Health services/ SU0 – Other - IVD assays

Article categories: PC0: IVD assays/ PC 21: Laboratory chemical

Environment contributing scenario(s):

ERC8a - Wide-dispersive indoor use of processing aids in open systems (Indoor use of processing aids by the public at large or professional use. Use (usually) results in direct release into the environment/sewage system.

Worker/Consumer contributing scenario(s):

PROC15 - Use as laboratory reagent

Subsequent service life exposure scenario(s): See waste scenario (Section 9.3.2.3)

Exposure scenario(s) of the uses leading to the inclusion of the substance into the article(s): not applicable

9.4.1.1. Description of the Activities and Technical Processes Covered in the Exposure Scenario

A description of the usage of the IVD assays is given in Section 9.3.1 combined for OPnEO and NPnEO.

Table 3 provides an overview of the products covered in each exposure scenario.

9.4.1.2. Environmental Contributing Scenario

9.4.1.2.1. Conditions of Use

The following table summarises the conditions of use as planned to be implemented at the UK sunset date. The amounts are given for the maximum usage in the UK over the review period based on the worst-case, i.e. that all substitutions are delayed.

Amount used, frequency and duration of use (or from service life)
▪ Total UK amount (kg/a): 48.65 (worst-case)
▪ Percentage of total amount used at regional scale: 100%
▪ Fraction of regional amount used at local scale: 0.004
▪ Maximum number of emission days (days/a): 360

▪ Wide-dispersive daily site amount (kg/day): 0.000598
▪ Type of release: Continuous release
Technical and organisational conditions and measures
▪ Wastewater is treated at municipal STP. ▪ Handling only by trained personnel
Conditions and measures related to sewage treatment plant
▪ Municipal STP: Yes (effectiveness: 45.5% of $OP_{equiv.}$)
▪ Discharge rate of STP: 2'000 m^3/day
▪ Application of the STP sludge on agricultural soil: Yes
Conditions and measures related to external treatment of waste (including article waste)
▪ Solid waste is collected and disposed of 'as if it was hazardous waste' ▪ Fraction of annual use expected in waste: 16% (7.88 kg/a)
Conditions and measures related to external recovery of waste (including article waste)
▪ No recovery.
Other conditions affecting environmental exposure
▪ Receiving surface water flow rate: 18'000 m^3/day
Additional good practice advice.
▪ communication to customers was amended to reflect the technical and organisational conditions and measures listed above.

9.4.1.2.2. RMMs Implemented

The fraction going to waste in this exposure scenario is calculated based on information on waste disposal from different instruments and assays as described in Section 9.3.1. including the RMMs described below.

All unused reagents in cartridges are disposed of as if they were hazardous solid waste (see waste scenario, Section 9.3.2.3 and Table 16). Note that most of these reagents are actually not classified as hazardous waste according to the waste regulations. However, instructions for waste disposal in communication to customers were adapted to indicate to dispose of this waste 'as if it was hazardous'.

It is not technically and practically feasible to implement further RMMs (see Section 9.6). However, releases will be continuously reduced by substitution (see Section 9.4.2).

Table 16. Environmental RMMs.

Compartment	RMM	Stated Effectiveness
Air	none (substance is not volatile)	n.a.
Water	collection and disposal of unused reagents in cartridges 'as if it was hazardous waste' Disposal as waste of a fraction of used products depending on the assays / instrument	16% of total used amount of OPnEO
Soil	none (no direct release to soil)	n.a.

9.4.1.2.3. Releases

OPnEO is used for different purposes in reagents for IVD assays. Therefore, the relevant environmental release category is ERC 8a - Wide-dispersive indoor use of processing aids in open systems (Indoor use of processing aids by the public at large or professional use). The default environmental release factors for ERC 8a are 100% release to air and water (before STP). In case of the use in IVD assays for laboratories / hospitals, soil needs to be considered at local and regional scale because of the possibility that sludge from STP is applied to soil (see Section 9.3.1.2).

However, substance and use-specific information is available to substantiate the fact that the default factors of ERC 8a for air and water are not applicable to the activities taking place at laboratories / hospitals.

Emission to air:

Due to the very low volatility of OPnEO ($Vp=1.8x10^{-14}$ mmHg, [1]) and the fact that no direct emissions to air arise at laboratories / hospitals, releases to air are not expected. The release factor to air was thus set to 0%. However, release to the air from STP through the aeration of the aerobic tank may still take place even if the release is expected to be very low.

Emission to wastewater:

Waste from different IVD assays and instruments was specifically assessed. An overall fraction going to waste was derived taking into account the RMMs already in place (see Section 9.4.1.2.2). Therefore, the default release factor to wastewater of 100% as foreseen for ERC 8a was adapted by subtracting the fraction going to waste (16%), leading to a final release factor of 84% of total OPnEO.

Emission to soil:

Due to the fact that no direct emissions to soil arise at the laboratories / hospitals and no disposal to soil from air is expected as no emissions to air are expected (see above), the release fraction to soil was set to 0%. However, due to the various locations of the laboratories / hospitals in the UK, the sludge generated by the STP may be applied to agricultural soil (see Section 9.3.1.2). In addition,

release to soil after STP via the air by way of deposition can still occur even if those are expected to be very small.

A summary of the initial and final release factors before STP selected for the exposure assessment is provided in Table 17.

Table 17. Local releases to the environment.

Release	Release factor estimation method	Explanation / Justification
Water	Standard release factor adapted with use-specific information	**Initial release factor (to STP):** 100% **Final release factor (to STP):** 84% (average over all products) **Local release rate to STP:** $5.10 \cdot 10^{-4}$ kg/day OPnEO ($1.70 \cdot 10^{-4}$ kg/day $OP_{equiv.}$) **Explanation / Justification:** Default release factor of ERC 8a adapted by the overall fraction being disposed of as waste
Air	Substance-specific information	**Initial release factor:** 0% **Final release factor:** 0% **Local release rate:** 0 kg/day **Explanation / Justification:** Substance is not volatile ($Vp=1.8 \cdot 10^{-14}$ mmHg, [1])
Soil	Standard release factor adapted with use-specific information	**Final release factor:** 0% **Explanation / Justification:** There is no direct release to soil from the laboratory. Release to soil before STP is therefore considered to be 0%.
Waste	See Section 9.3.2.3 (waste scenarios)	**Final release factor (to waste):** 16% **Local release rate to STP (from waste):** 0.000255 g/day OPnEO (0.000085 g/day $OP_{equiv.}$) **Explanation / Justification:** Specific evaluation of waste streams (see Section 9.3.2.3, waste scenarios)

Releases to waste

Release factor to waste from the process:

During the use at the laboratories / hospitals, empty cartridges / of reagents, and waste of used reagents from some instruments are collected and disposed of as waste. The overall fraction going to waste was derived considering the RMMs that are already in place (see Section 9.4.1.2.2).

Release factor to waste from on-site treatment:

Usually, no on-site treatment of wastewater is taking place (see Section 9.6). Therefore, on-site treatment is not considered in the assessment.

9.4.1.2.4. Exposure and Risks for the Environment

Table 18. Exposure concentrations and risks for the environment – on local and regional scale.

Protection target	Unit	Exposure concentration local in $OP_{equiv.}$	Exposure concentration regional in $OP_{equiv.}$	TOTAL Exposure concentration local in $OP_{equiv.}$
Sewage treatment plant	µg/L	0.0597	Not applicable	**0.0597**
Freshwater	µg/L	0.00597	$6.19 \cdot 10^{-6}$	**0.00598**
Sediment (freshwater)	mg/kg	0.000145	$4.88 \cdot 10^{-7}$	**0.000145**
Marine water	µg/L	0.000597	$6.26 \cdot 10^{-6}$	**0.000603**
Sediment (marine water)	mg/kg	0.0000145	$2.26 \cdot 10^{-7}$	**0.0000147**
Agricultural soil	mg/kg	0.0000458	$9.02 \cdot 10^{-7}$	**0.0000467**
Air	pg/m3	0.000167	$2.60 \cdot 10^{-8}$	**0.000167**

Table 19. Exposure concentrations and risks for the environment for ES 1 during waste life stage - on local and regional scale.

Protection target	Unit	Exposure concentration (C_{local}) in $OP_{equiv.}$	Exposure concentration ($C_{regional}$) in $OP_{equiv.}$
Freshwater	µg/L	$2.38 \cdot 10^{-6}$	$9.62 \cdot 10^{-7}$
Sediment (freshwater)	mg/kg	$5.79 \cdot 10^{-8}$	$2.34 \cdot 10^{-8}$
Marine water	µg/L	$2.38 \cdot 10^{-7}$	$9.62 \cdot 10^{-8}$

Protection target	Unit	Exposure concentration (C_{local}) in $OP_{equiv.}$	Exposure concentration ($C_{regional}$) in $OP_{equiv.}$
Sediment (marine water)	mg/kg	$5.79 \cdot 10^{-9}$	$2.34 \cdot 10^{-9}$
Sewage Treatment Plant	µg/L	$2.38 \cdot 10^{-5}$	$9.62 \cdot 10^{-6}$
Agricultural Soil	mg/kg	$1.69 \cdot 10^{-8}$	$6.38 \cdot 10^{-9}$

PEC regional is based on the use applied for by RDL. Please refer to Section 9.3.2.4 for calculation of PEC regional.

Remarks on measured exposure:

PEC after STP have not been measured.

Comparative calculation for a big laboratory / hospital:

A calculation was performed using the total daily local use amount calculated for a big laboratory / hospital (release of 4.793 g/day OPnEO for total of all assays, see details in supporting document SD3a_CSR_Usage_Releases_OPnEO_RDL_Use3_CONFIDENTIAL) to discuss the possible variability that could be observed locally.

Table 20 presents the calculated PEC for a big laboratory / hospital. When the standard scenario was applied to the big laboratory / hospital a risk was identified ('initial scenario'). Therefore, the calculation was refined ('refined scenario') using a separate local scenario based on information from the specific location of the big laboratory / hospital (see SD2b_CSR_Model_description_partII_RDL_Use3). When comparing the calculated PEC local for the refined scenario with the PEC local obtained with the wide-dispersive approach (see Table 18), it can be concluded that the PEC local is ca. 20 times lower for all compartments for a big laboratory in comparison with an average-size laboratory. This is based on the worst-case assumptions for the average-sized laboratory (less population, smaller STP, less river water flow) compared to the situation for the big laboratory with the local scenario.

Table 20. Exposure concentrations on local scale for a big laboratory / hospital.

		Big laboratory			
Protection target	**Unit**	**Exposure concentration local in OP_{equiv} (initial scenario)**	**Exposure concentration local in $OP_{equiv.}$ (refined scenario)**	**Exposure concentration regional in $OP_{equiv.}$.**	**TOTAL Exposure concentration local in $OP_{equiv.}$ (refined sce.)**
Sewage treatment plant	µg/L	0.486	0.00252	Not applicable	**0.00252**

		Big laboratory			
Protection target	**Unit**	**Exposure concentration local in OP_{equiv} (initial scenario)**	**Exposure concentration local in $OP_{equiv.}$ (refined scenario)**	**Exposure concentration regional in $OP_{equiv..}$**	**TOTAL Exposure concentration local in $OP_{equiv.}$ (refined sce.)**
Freshwater	µg/L	0.0486	0.000219	$6.19 \cdot 10^{-6}$	**0.000225**
Sediment (freshwater)	mg/kg	0.00118	$5.32 \cdot 10^{-6}$	$4.88 \cdot 10^{-7}$	**$5.81 \cdot 10^{-6}$**
Marine water	µg/L	0.00486	$2.52 \cdot 10^{-5}$	$6.26 \cdot 10^{-6}$	**$3.14 \cdot 10^{-5}$**
Sediment (marine water)	mg/kg	0.000118	$6.13 \cdot 10^{-7}$	$2.26 \cdot 10^{-7}$	**$8.39 \cdot 10^{-}$**
Agricultural soil	mg/kg	0.000373	$1.93 \cdot 10^{-6}$	$9.02 \cdot 10^{-7}$	**$2.83 \cdot 10^{-6}$**
Air	pg/m^3	0.00136	$7.05 \cdot 10^{-6}$	$2.60 \cdot 10^{-8}$	**$7.08 \cdot 10^{-6}$**

Conclusion on risk characterisation:

Risk characterisation was not assessed because no threshold can be derived for the endpoint ’endocrine disrupting properties of the degradation products’ for the substance. Instead, risk / exposure minimisation are demonstrated in this CSR. PEC per site are compared with Environmental Quality Standards and PNEC values as an indication of remaining risk in Section 10.

9.4.1.3. Workers Contributing Scenario

Not required

9.4.2. Minimisation of Releases to the Environment and Expected Evolution over the Review Period

In this section, the aim of the applicant is to demonstrate that emissions and releases to the environment to and after STP from the activities covered in Use 3 are minimised as far as practically and technically feasible. In addition, the aim is to provide an overview of the expected evolution of the releases of OPnEO to wastewater from the UK sunset date (the 30th of June 2022) to the end of the review period (the 4th of January 2028).

From the UK sunset date on the 30th of June 2022 till the end of the review period, the total release of OPnEO to wastewater at the downstream sites is expected to vary mainly due to:

- Change in quantities of OPnEO required for the IVD-assays due to evolution in the sales of assays thereby influencing the quantities of OPnEO used and released to wastewater by the downstream users (laboratories / hospitals).

- Planned substitutions of OPnEO in the IVD assays leading to a decrease of OPnEO used and

released to wastewater.

Minimisation of releases to wastewater is discussed in Section 9.4.2.1.
Minimisation of release of $OP_{equiv.}$ after STP to surface water and soil is discussed in Section 9.4.2.2.

9.4.2.1. Minimisation of Releases to Wastewater for the Wide-Dispersive Uses

For the wide-dispersive uses i.e. at laboratories / hospitals, the total used amounts were deduced from the total imported amounts in the UK. Based on this information, the total release to wastewater from the wide-dispersive uses was estimated assuming a release to wastewater of 84% of the total used amount considering the overall fraction going to waste. The latter was derived from specific information for different IVD assays and instruments considering the RMMs already in place.

The implementation of further RMMs is not feasible as discussed in Section 9.6.

As further RMMs after the UK sunset date are not feasible, the main measure to reduce the release of OPnEO to wastewater from the downstream users i.e. laboratories / hospitals is the substitution of OPnEO in the formulated reagents. The effect of this measure is delayed in comparison with the release from the formulation process due to the shelf life of the reagents on the market. As a worst-case it is assumed that from the completion of substitution at the production site until the end of the shelf life of the assay, the release from the assays with OPnEO remains constant. However, it is likely that stocks of ‘old’ product will be replaced by new products earlier than the end of the shelf life, thus reducing emissions earlier.

Figure 6 presents the expected evolution of the total annual release of OPnEO between 2017 until the end of 2027 for the downstream sites considering substitutions and shelf life of the formulated reagents. Calculations are based on data from the EU dossier and scaled to the UK (see section 9.2.2.1 for details).

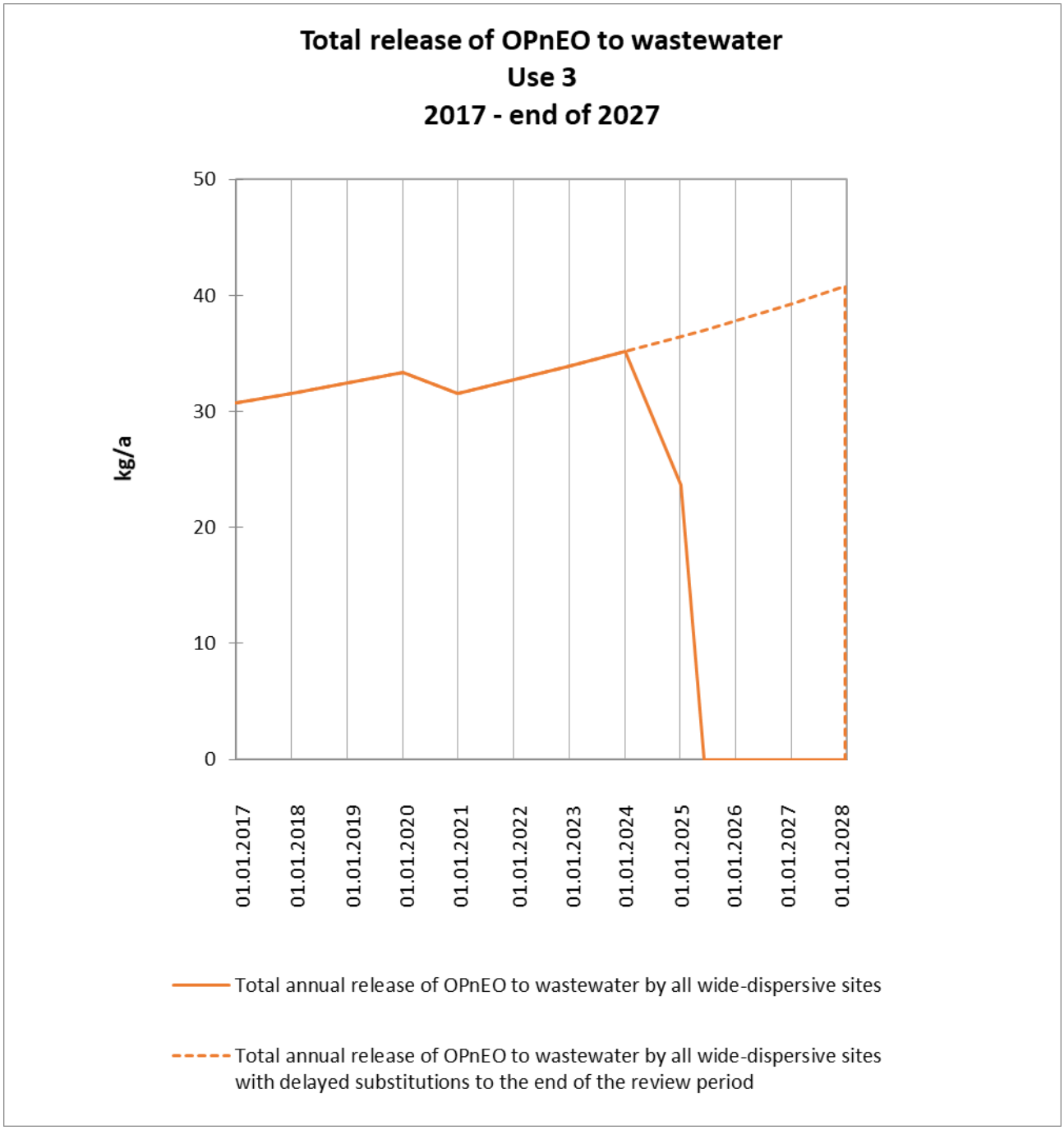

Figure 6. Evolution of the total annual release of OPnEO between 2017 until the end of 2027 for the downstream sites considering planned substitutions, sales development, and the shelf life of the reagents.

If the substitutions are completed in time in the formulated reagents, the total release of OPnEO to wastewater at the downstream sites would initially further increase from 33.33 kg/a at the UK sunset date to reach a maximum of 35.16 kg/a in 2024 due to growth in the sales figures. After that, the release will decrease and will be 1.04 g/a on 1st of June 2025 (0 g/a on 1st of April 2026) in-line with the delay due to the shelf life of the products. However, if the substitutions are delayed to the end of the review period for all formulation activities, a maximum total annual release of 40.77 kg/a to

wastewater from all wide-dispersive uses could potentially be reached as a worst-case until the end of the review period. Even though there is a certain risk of delay of substitution projects due to potential technical or regulatory difficulties and some delays have already occurred (see AoA), a delay of all projects until the end of the review period is highly unlikely.

9.4.2.2. Minimisation of Releases after STP to Surface Water and Soil from Wide-Dispersive Uses

As for the release to STP, two cases have to be considered regarding the expected decrease in the total release to surface water and soil in $OP_{equiv.}$ by the activities covered in Use 3 over time until the end of the review period considering the risk management measures implemented before the EU sunset date (4th of January 2021) and sales development:

- 'All substitutions completed as planned': Expected decrease in the total release in $OP_{equiv.}$ over time considering the planned substitutions and risk management measures at the downstream sites, which were implemented by the EU sunset date.

- 'All substitutions delayed': Expected development in the total release in $OP_{equiv.}$ over time considering that all planned substitutions at the production sites are delayed towards the end of the review period leading to emissions at downstream sites until the end of the review period as a worst-case; Risk management measures were implemented by the EU sunset date at the downstream sites as for the case 'All substitutions completed as planned'.

Figure 7 presents the expected evolution of the total annual release to surface water in $OP_{equiv.}$ between 2017 until the end of 2027 for the downstream sites considering substitutions and shelf life of the products. The same trend is also applicable to release to soil via application of sludge to agricultural soil. Expected and worst-case releases to surface water after STP and soil per year for 2022 and over the course of the review period are given in Table 21.

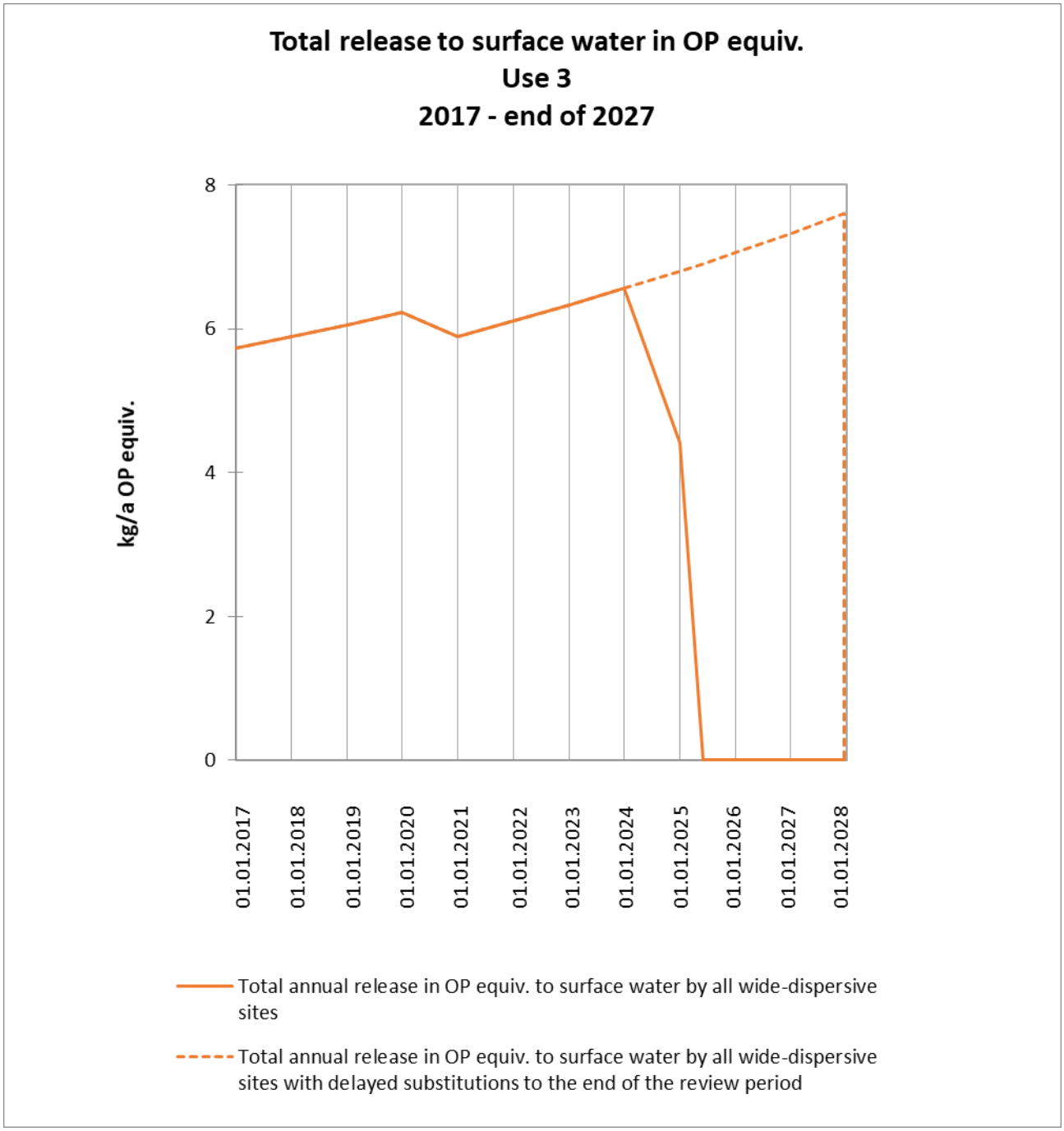

Figure 7. Evolution of the total annual release to surface water in $OP_{equiv.}$ from 2017 until the end of 2027 for the downstream sites considering planned substitutions, sales development, and the shelf life of the reagents.

If the substitutions are completed in time in the formulated reagents, the total release to surface water in $OP_{equiv.}$ at the downstream sites would initially further increase from 6.22 kg/a $OP_{equiv.}$ at the UK sunset date to reach a maximum of 6.56 kg/a in 2024 due to growth in the sales figures. After that, the release will decrease and will be 0.19 g/a on 1st of June 2025 (0 g/a on 1st of April 2026) in-line with the delay due to the shelf life of the products. However, if the substitutions are delayed towards the end of the review period for all formulation activities, a maximum total annual release of 7.61

kg/a OP_{equiv} to surface water from all wide-dispersive uses could potentially be reached as a worst-case until the end of the review period. Even though there is a certain risk of delay of substitution projects due to potential technical or regulatory difficulties and some delays have already occurred (see AoA), a delay of all projects until the end of the review period is highly unlikely.

Table 21. Expected and worst-case releases to surface water after STP and soil (from application of sewage sludge) per year in kg /a OP_{equiv}. from 2022 until the end of 2027 considering RMMs implemented at the EU sunset date.

USE 3	Scenario	Unit	Downstream uses release to surface water	Downstream uses release to soil*
Release to surface water / soil after STP at sunset date (30th of June 2022)	**Expected release considering substitutions**	kg/a $OP_{equiv.}$	6.22	5.19
	Max total releases with delayed substitutions	kg/a $OP_{equiv.}$	6.22	5.19
Release to surface water / soil after STP at the end of review period (end of 2027)	**Expected release considering substitutions**	kg/a $OP_{equiv.}$	0	0
	Max total releases with delayed substitutions	kg/a $OP_{equiv.}$	7.61	6.35
Total release to surface water / soil after STP over the review period (2022-end of 2027)	**Expected release considering substitutions**	kg/5.5a $OP_{equiv.}$	20.41	17.0
	Max total releases with delayed substitutions	kg/5.5a $OP_{equiv.}$	44.79	37.3

* Releases to soil are worst-case as 100% of sludge is assumed to be applied to soil (see Section 9.3.2.1).

9.4.3. Results of the Monitoring Data and Validation of the 'Multifate' Model

A monitoring campaign was not performed for the use at downstream sites involving OPnEO addressed in this CSR. However, a monitoring campaign was conducted for OPnEO for the protein production processes covered in Use 4[4] of the EU dossier which served as a basis to validate the

[4] Use 4 - Use of Octyl- and Nonylphenolethoxylates in the production of proteins and the conjugation of latex beads, both being used as components or for the production of components of in vitro diagnostic (IVD) assays, research or quality control products and other, e.g. analytical applications

calculations made using the 'Multifate' model. The comparison of monitoring data with the modelled data confirmed that the assumptions used in the model 'Multifate' were very conservative (e.g., 100% of OPnEO released to wastewater; no complete mineralisation), as the modelled concentrations were always by a factor of 30 to 440 higher compared to the measured data. Detailed data of the validation are given in the CSR of Use 4 of the EU dossier in section 9.4.5. 'Results of the Monitoring Data and Validation of the 'Multifate' Model'[5]

OPnEO concentrations measured in liquid waste from IVD instruments are discussed in Section 9.3.1.1.

[5] Link to CSR of Use 4: https://echa.europa.eu/documents/10162/0775aa16-4c55-77b6-0d94-013c5ffae586

9.5. Exposure Assessment for NPnEO

- ⇨ Considering the RMMs in place, the total release of NPnEO to **wastewater at the downstream sites is 0.18 kg/a** for the use applied for at the UK sunset date, assuming that all substitutions are delayed (worst-case).
- ⇨ The **maximum annual release of NPnEO** over the course of the review period **of 0.18 kg/a** is reached at the UK sunset date, assuming that all substitutions are delayed (worst-case). After this date, the release will constantly decrease, even if the substitutions are delayed.

9.5.1. Exposure Scenario 1: PW1 – NPnEO - Use in IVD Assays for Laboratories / Hospitals

Sector of use: SU20 – Health services/ SU0 – Other - IVD assays

Article categories: PC0: IVD assays/ PC 21: Laboratory chemical

Environment contributing scenario(s):

ERC8a - Wide-dispersive indoor use of processing aids in open systems (Indoor use of processing aids by the public at large or professional use. Use (usually) results in direct release into the environment/sewage system)

Worker/Consumer contributing scenario(s):

PROC15 - Use as laboratory reagent

Subsequent service life exposure scenario(s): See waste scenario (Section 9.3.2.3)

Exposure scenario(s) of the uses leading to the inclusion of the substance into the article(s): not applicable

9.5.1.1. Description of the Activities and Technical Processes Covered in the Exposure Scenario

A description of the usage of the IVD assays is given in Section 9.3.1 combined for OPnEO and NPnEO. Table 3 provides an overview of the products covered in each exposure scenario.

9.5.1.2. Environmental Contributing Scenario

9.5.1.2.1. Conditions of Use

The following table summarises the conditions of use as planned to be implemented at the UK sunset date. The amounts are given for the maximum usage in the UK over the review period based on the worst-case, i.e. that all substitutions are delayed. In case of NPnEO, the maximum usage over the review period will be reached at the UK sunset date and will subsequently constantly decrease over time.

Amount used, frequency and duration of use (or from service life)
▪ Total UK amount (kg/a): 0.39
▪ Percentage of total UK amount used at regional scale: 100%
▪ Fraction of regional amount used at local scale: 0.025

▪ Maximum number of emission days (days/a): 360
▪ Wide-dispersive daily site amount (kg/day): 0.0000268
▪ Type of release: Continuous release
Technical and organisational conditions and measures
▪ Wastewater is treated at municipal STP. ▪ Handling only by trained personnel
Conditions and measures related to sewage treatment plant
▪ Municipal STP: Yes (effectiveness: 75.3% of $NP_{equiv.}$)
▪ Discharge rate of STP: 2'000 m^3/day
▪ Application of the STP sludge on agricultural soil: Yes
Conditions and measures related to external treatment of waste (including article waste)
▪ Solid waste is collected and disposed of 'as if it was hazardous waste' ▪ Fraction of daily/annual use expected in waste: 53% 0.21 kg/a
Conditions and measures related to external recovery of waste (including article waste)
▪ No recovery.
Other conditions affecting environmental exposure
▪ Receiving surface water flow rate:18'000 m^3/day
Additional good practice advice.
▪ communication to customers was amended to reflect the technical and organisational conditions and measures listed above.

9.5.1.2.2. RMMs Implemented

The fraction going to waste in this exposure scenario is calculated based on information on waste disposal from different instruments and assays as described in Section 9.3.1. including the RMMs described below.

All unused reagents in cartridges / are disposed of as if they were hazardous solid waste (see waste scenario, Section 9.3.2.3 and Table 22). Note that most of these reagents are actually not classified as hazardous waste according to the waste regulations. However, instructions for waste disposal in communication to customers were adapted to indicate to dispose of this waste 'as if it was hazardous'. It is not technically and practically feasible to implement further RMMs (see Section 9.6). However, releases will be continuously reduced by substitution (see Section9.5.2).

Table 22. Environmental RMMs

Compartment	RMM	Stated Effectiveness
Air	None (substance is not volatile)	n.a.
Water	Collection and disposal of unused reagents in cartridges / 'as if it was hazardous waste' Disposal as waste of a fraction of used products depending on the assays / instrument	53% of total used amount of NPnEO
Soil	None (no direct release to soil)	n.a.

9.5.1.2.3. Releases

NPnEO is used for different purposes in reagents for IVD assays. Therefore, the relevant environmental release category is ERC 8a - Wide-dispersive indoor use of processing aids in open systems (indoor use of processing aids by the public at large or professional use. The default environmental release factors for ERC 8a are 100% release to air and water (before STP). In case of the use in IVD assays for laboratories / hospitals, soil needs to be considered at regional and local scale because of the possibility that sludge from STP is applied to soil (see Section 9.3.1.2).

However, substance and use-specific information is available to substantiate the fact that the default factors of ERC 8a for air and water are not applicable to all the activities taking place at laboratories / hospitals.

Emission to air:

Due to the very low volatility of NPnEO (Vp=1.78x10^{-7} mmHg, given for short chain 4-NP1EO; as the vapour pressure is expected to decrease with increasing length of the ethoxylate chain) the vapour pressure of NPnEO is expected to be very low [1]) and the fact that no direct emissions to air arise at laboratories / hospitals, releases to air are not expected. The release factor to air was thus set to 0%. However, release to the air from STP through the aeration of the aerobic tank may still take place even if the release is expected to be very low.

Emission to wastewater:

Waste from different IVD assays and instruments was specifically assessed. An overall fraction going to waste was derived taking into account the RMMs already in place (see Section 9.5.1.2.2). Therefore, the default release factor to wastewater of 100% as foreseen for ERC 8a was adapted by subtracting the fraction going to waste (53%), leading to a final release factor of 47% of total NPnEO.

Emission to soil:

Due to the fact that no direct emissions to soil arise at the laboratories / hospitals and no disposal to soil from air is expected as no emissions to air are expected (see above), the release fraction to soil was set to 0%. However, due to the various location of the laboratories / hospitals in the UK, the

sludge generated by the STP may be applied to agricultural soil (see Section 9.3.1.2). In addition, release to soil after STP via the air by way of deposition can still occur even if those are expected to be very small.

A summary of the initial and final release factors before STP selected for the exposure assessment is provided in Table 23.

Table 23. Local releases to the environment.

Release	Release factor estimation method	Explanation / Justification
Water	Standard release factor adapted with use-specific information	**Initial release factor (to STP):** 100% **Final release factor (to STP):** 47% (average over all products) **Local release rate to STP:** $1.157 \cdot 10^{-5}$ kg/day NPnEO (6.65×10^{-7} kg/day $NP_{equiv.}$) **Explanation / Justification:** Default release factor of ERC 8a adapted by the overall fraction being disposed of as waste
Air	Substance-specific information	**Initial release factor:** 0% **Final release factor:** 0% **Local release rate:** 0 kg/day **Explanation / Justification:** Substance is not volatile (Vp <<1.78×10^{-7} mmHg, [1])
Soil	Standard release factor adapted with use-specific information	**Final release factor:** 0% **Explanation / Justification:** There is no direct release to soil from the laboratory. Release to soil before STP is therefore considered to be 0%.
Waste	See Section 9.3.2.3 (waste scenarios)	**Final release factor (to waste):** 53% **Local release rate to STP (from waste):** $6.66 \cdot 10^{-6}$ g /day NPnEO (2.22×10^{-6} g/day $NP_{equiv.}$) **Explanation / Justification:** Specific evaluation of waste streams (see Section 9.3.2.3, waste scenarios)

Releases to waste

Release factor to waste from the process:

During the use at the laboratories / hospitals, empty cartridges of reagents, and waste of used reagents from some instruments are collected and disposed of as waste. The overall fraction going to waste was derived taking into account the RMMs already in place (see Section 9.5.1.2.2).

Release factor to waste from on-site treatment:

Usually, no on-site treatment of wastewater is taking place (see Section 9.6). Therefore, on-site treatment is not considered in the assessment.

9.5.1.2.4. Exposure and Risks for the Environment

Table 24. Exposure concentrations and risks for the environment – on local and regional scale.

Protection target	Unit	Exposure concentration local in $NP_{equiv.}$	Exposure concentration regional in $NP_{equiv.}$	TOTAL Exposure concentration local in $NP_{equiv.}$
Sewage treatment plant	µg/L	$4.76 \cdot 10^{-4}$	not applicable	**$4.76 \cdot 10^{-4}$**
Freshwater	µg/L	$4.76 \cdot 10^{-5}$	$5.27 \cdot 10^{-11}$	**$4.76 \cdot 10^{-5}$**
Sediment (freshwater)	mg/kg	$3.87 \cdot 10^{-6}$	$1.41 \cdot 10^{-11}$	**$3.87 \cdot 10^{-6}$**
Marine water	µg/L	$4.76 \cdot 10^{-6}$	$1.90 \cdot 10^{-7}$	**$4.95 \cdot 10^{-6}$**
Sediment (marine water)	mg/kg	$3.87 \cdot 10^{-7}$	$1.76 \cdot 10^{-6}$	**$2.15 \cdot 10^{-6}$**
Agricultural soil	mg/kg	$8.24 \cdot 10^{-7}$	$1.53 \cdot 10^{-10}$	**$8.24 \cdot 10^{-7}$**
Air	pg/m^3	$8.67 \cdot 10^{-6}$	$1.04 \cdot 10^{-12}$	**$8.67 \cdot 10^{-6}$**

Table 25. Exposure concentrations and risks for the environment for ES 1 during waste life stage - on local and regional scale.

Protection target	Unit	Exposure concentration (Clocal) in $NP_{equiv.}$	Exposure concentration (Cregional) in $NP_{equiv.}$
Freshwater	µg/L	$2.74 \cdot 10^{-8}$	$1.89 \cdot 10^{-9}$
Sediment (freshwater)	mg/kg	$2.23 \cdot 10^{-9}$	$1.54 \cdot 10^{-10}$
Marine water	µg/L	$2.74 \cdot 10^{-9}$	$3.27 \cdot 10^{-10}$
Sediment (marine water)	mg/kg	$2.23 \cdot 10^{-10}$	$2.66 \cdot 10^{-11}$
Sewage Treatment Plant	µg/L	$2.74 \cdot 10^{-7}$	$3.27 \cdot 10^{-8}$
Agricultural soil	mg/kg	$4.72 \cdot 10^{-10}$	$7.69 \cdot 10^{-12}$

PEC regional is based on the use applied for by RDL. Please refer to Section 9.3.2.4 for calculation of PEC regional.

Remarks on measured exposure:

PEC after STP have not been measured (see Section 9.3.2.5.2).

Comparative calculation for a big laboratory/hospital and blood bank:

To discuss the possible variability that could be observed locally, two additional calculations were performed using the total daily local use amounts calculated for:

- A big laboratory / hospital and
- A big blood bank.

These two cases were addressed separately. As the use of big laboratories and big blood bank may differ significantly (laboratory: Several assays to measure a range of different parameters, blood bank: Limitation to immunological parameters for the detection of HIV).

Table 26 presents the calculated PEC for a big laboratory / hospital and a big blood bank. When comparing the calculated PEC local with the PEC local obtained with the wide-dispersive approach (see Table 24), it can be concluded that the PEC local can be ca. 3 times higher for all compartments for a big laboratory in comparison with an average-size laboratory. For a big blood bank, the PEC local can be ca. 37 times higher in comparison with an average-size laboratory. Note that an average-size blood bank has similar releases to an average-size laboratory (see supporting document SD3b_CSR_Data_collected_NPnEO_RDL_Use3_CONFIDENTIAL). The PEC local of a big blood bank for $NP_{equiv.}$ is however similar to the PEC local for $OP_{equiv.}$ of an average-size laboratory. This

is based on the worst-case assumption that such a big laboratory / blood bank would also be located in a small town of 67'000 inhabitants.

Table 26. Exposure concentrations on local scale for a big laboratory / hospital and a big blood bank.

Protection target	**Unit**	**Big laboratory**			**Big blood bank**		
		Exposure concen-tration local in $NP_{equiv.}$	**Exposure concentration regional in $NP_{equiv.}$**	**TOTAL Exposure concentration local in $NP_{equiv.}$**	**Exposure concen-tration local in $NP_{equiv.}$**	**Exposure concentration regional in $NP_{equiv.}$**	**TOTAL Exposure concentration local in $NP_{equiv.}$**
Sewage treatment plant	µg/L	$1.58 \cdot 10^{-3}$	not applicable	**0.00158**	$1.75 \cdot 10^{-2}$	not applicable	**0.0175**
Freshwater	µg/L	$1.58 \cdot 10^{-4}$	$5.27 \cdot 10^{-11}$	**0.000158**	$1.75 \cdot 10^{-3}$	$5.27 \cdot 10^{-11}$	**0.00175**
Sediment (freshwater)	mg/kg	$1.28 \cdot 10^{-5}$	$1.41 \cdot 10^{-11}$	**0.0000128**	$1.42 \cdot 10^{-4}$	$1.41 \cdot 10^{-11}$	**0.000142**
Marine water	µg/L	$1.57 \cdot 10^{-5}$	$1.90 \cdot 10^{-7}$	**0.0000159**	$1.75 \cdot 10^{-4}$	$1.90 \cdot 10^{-7}$	**0.000175**
Sediment (marine water)	mg/kg	$1.28 \cdot 10^{-6}$	$1.76 \cdot 10^{-6}$	**$3.04 \cdot 10^{-6}$**	$1.42 \cdot 10^{-5}$	$1.76 \cdot 10^{-6}$	**0.0000142**
Agricultural soil	mg/kg	$2.73 \cdot 10^{-6}$	$1.53 \cdot 10^{-10}$	**0.00000273**	$3.01 \cdot 10^{-5}$	$1.53 \cdot 10^{-10}$	**0.0000301**
Air	pg/m^3	$2.87 \cdot 10^{-5}$	$1.04 \cdot 10^{-12}$	**0.0000287**	$3.18 \cdot 10^{-4}$	$1.04 \cdot 10^{-12}$	**0.000318**

Conclusion on risk characterisation:

Risk characterisation was not assessed because no threshold can be derived for the endpoint 'endocrine disrupting properties of the degradation products' for the substance. Instead, risk and exposure minimisation are demonstrated in this CSR. PEC per site is compared with Environmental Quality Standards and PNEC values as an indication of remaining risk in Section 10.

9.5.1.3. Workers Contributing Scenario

Not required

9.5.2. Minimisation of Releases to the Environment and Expected Evolution over the Review Period

In this section, the aim of the applicant is to demonstrate that emissions and releases to the environment to and after STP from the activities covered in Use3 are minimised as far as practically and technically feasible. In addition, the aim is to provide an overview of the expected evolution of the releases of NPnEO to wastewater from the UK sunset date (the 30th of June 2022) to the end of the review period (the 4th of January 2028).

From the UK sunset date on the 30th of June 2022 till the end of the review period, the total release of NPnEO to wastewater at the downstream sites is expected to vary mainly due to:

- Change in quantities of NPnEO required for the IVD-assays due to evolutions in the sales of assays thereby influencing the quantities of NPnEO used and released to wastewater by the downstream users (laboratories / hospitals / blood banks).

- Planned substitutions of NPnEO in IVD assays leading to a decrease of NPnEO used and released to wastewater.

Minimisation of releases to wastewater is discussed in Section9.5.2.1.
Minimisation of release of $NP_{equiv.}$ after STP to surface water and soil is discussed in Section9.5.2.2.

9.5.2.1. Minimisation of Releases to Wastewater for the Wide-Dispersive Uses

For the wide-dispersive uses i.e. at laboratories / hospitals / blood banks, the total used amounts were deduced from the total imported amounts in the UK. Based on this information, the total release to wastewater from the wide-dispersive uses was estimated assuming a release to wastewater of 47% of the total used amount considering the overall fraction going to waste (53%). The latter was derived from specific information for different IVD assays and instruments taking into account the RMMs already in place.

The implementation of further RMMs is not feasible as discussed in Section 9.6.

As further RMMs after the UK sunset date are not feasible, the main measure to reduce the release of NPnEO to wastewater from the downstream users i.e. laboratories / hospitals / blood banks is the substitution of NPnEO in the reagents. The effect of this measure is delayed in comparison with the release from the formulation processes due to the shelf life of the products on the market. As a worst-case it is assumed that from the completion of substitution at the production site until the end of the shelf life of the assay, the release from the assays with NPnEO remains constant. However, it is likely that stocks of ‘old’ product will be replaced by new products earlier than the end of the shelf life, thus reducing emissions earlier. Figure 8 presents the expected evolution of the total annual release of NPnEO between 2017 and until the end of 2027 for the downstream sites considering substitutions and shelf life of the products. Calculations are based on data from the EU dossier and scaled down to the UK (see section 9.2.3.1 for details).

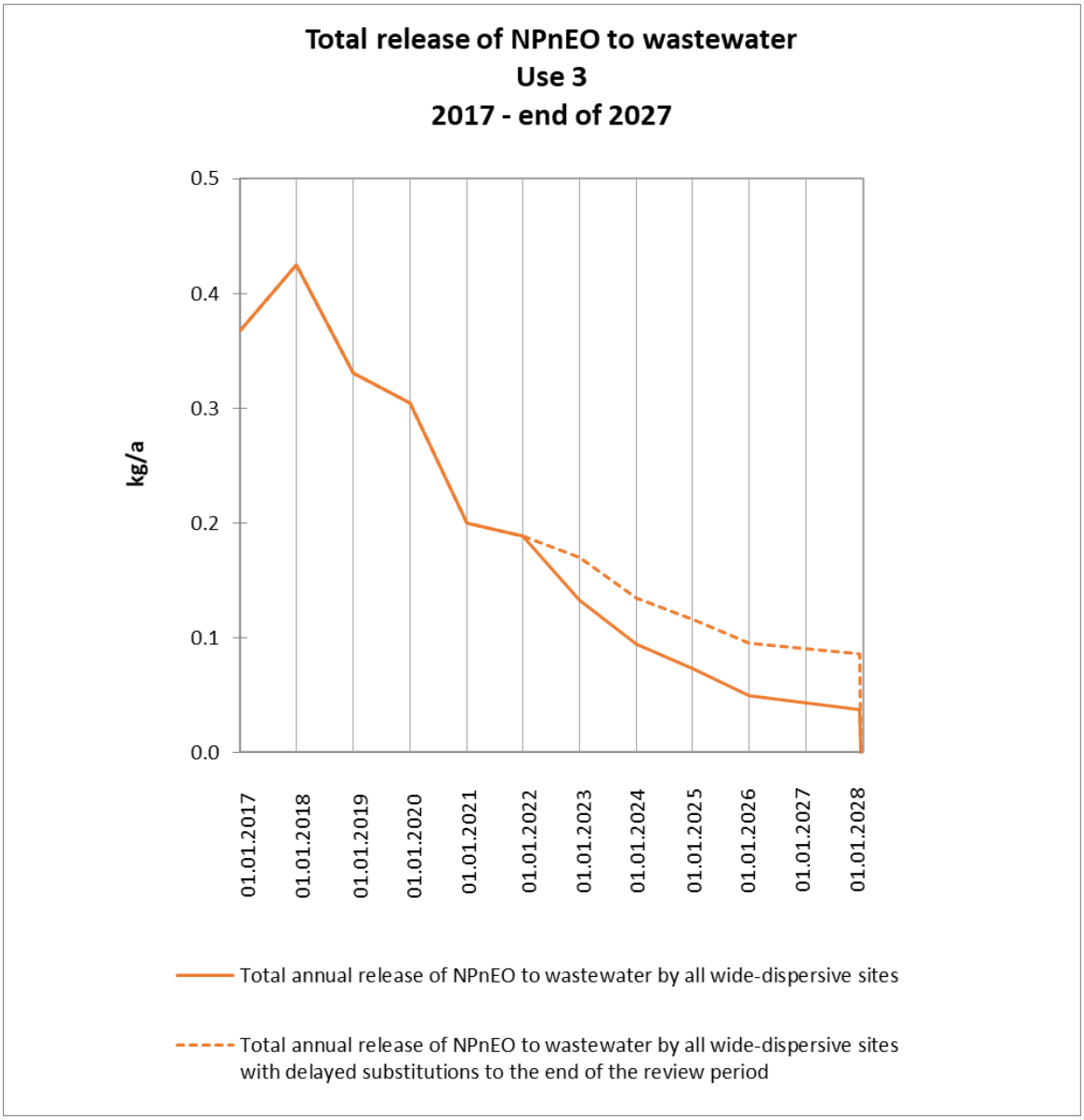

Figure 8. Evolution of the total annual release of NPnEO between 2017 until the end of 2027 for the downstream sites considering planned substitutions, sales development, and the shelf life of the products.

If the substitutions are completed in time, the total release of NPnEO to wastewater at the downstream sites should decrease from 0.16 kg/a at the UK sunset date to reach 0 at the end of the review period in-line with the delay due to the shelf life of the products. However, if the substitutions are delayed to the end of the review period for all formulation activities, a maximum total annual release of 0.18 kg/a to wastewater from all wide-dispersive uses could potentially be reached as a worst-case at the UK sunset date. Even though there is a certain risk of delay of substitution projects due to potential technical or regulatory difficulties and some delays have already occurred (see AoA), a delay of all projects until the end of the review period is highly unlikely.

9.5.2.2. Minimisation of Releases after STP to Surface Water and Soil from Wide-Dispersive Uses

As for the release to STP, two cases have to be considered regarding the expected decrease in the total release to surface water and soil in $NP_{equiv.}$ by the activities covered in Use 3 over time until the end of the review period considering the risk management measures implemented until the EU sunset date and sales development:

- 'All substitutions completed as planned': Expected decrease in the total release in $NP_{equiv.}$ over time considering the planned substitutions and risk management measures at the downstream sites, which were implemented by the EU sunset date.

- 'All substitutions delayed': Expected development in the total release in $NP_{equiv.}$ over time considering that all planned substitutions at the production sites are delayed towards the end of the review period leading to emissions at downstream sites until the end of the review period as a worst-case; Risk management measures were implemented by the EU sunset date at the downstream sites as for the case 'All substitutions completed as planned'.

Figure 9 presents the expected evolution of the total annual release to surface water in $NP_{equiv.}$ between 2017 until the end of 2027 for the downstream sites considering substitutions and shelf life of the products. The same trend is also applicable to release to soil via application of sludge to agricultural soil. Expected and worst-case releases to surface water after STP and soil per year for the UK sunset date and over the course of the review period are given in Table 27.

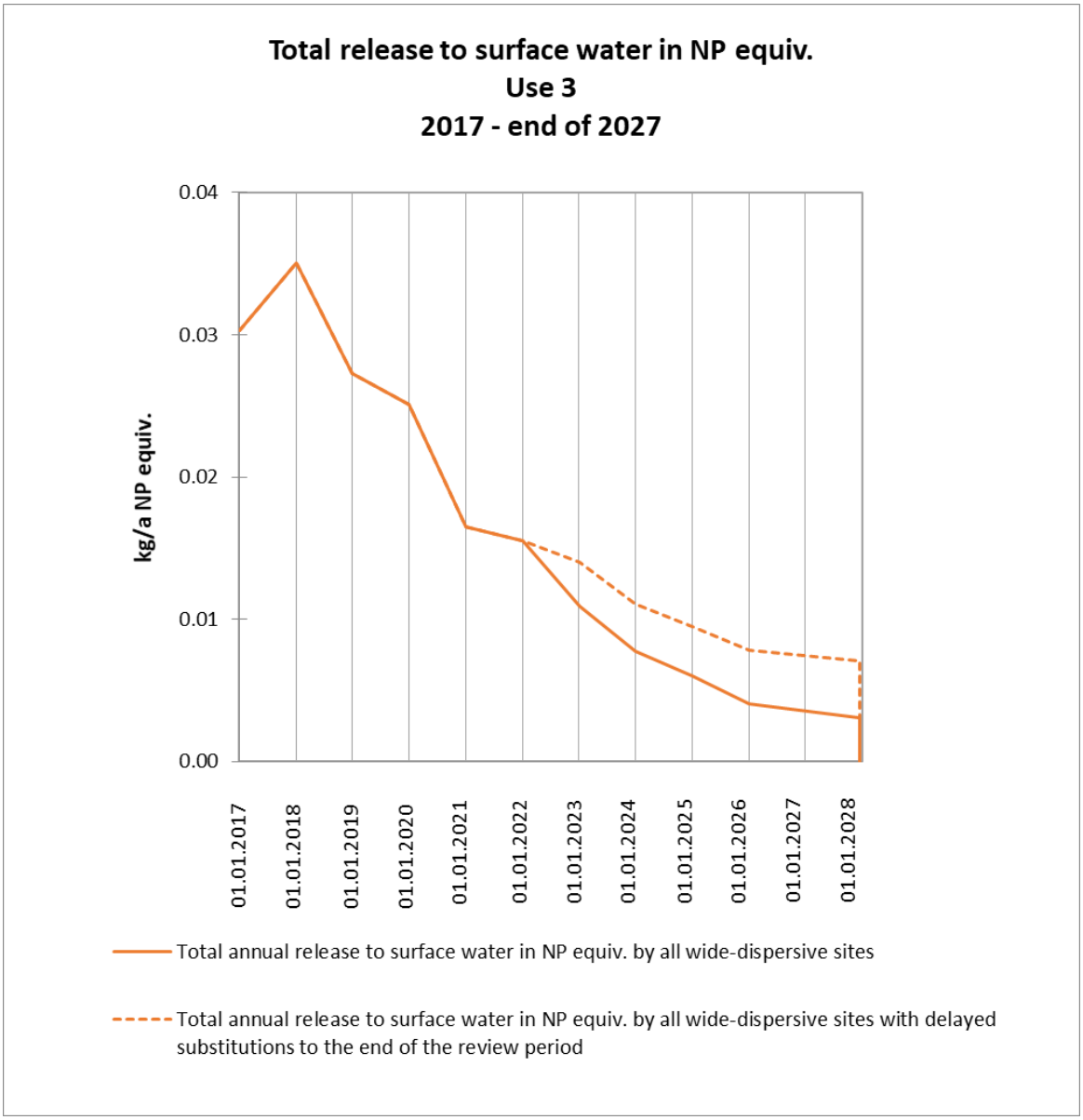

Figure 9. Evolution of the total annual release to surface water in $NP_{equiv.}$ from 2017 until the end of 2027 for the downstream sites considering planned substitutions, sales development, and the shelf life of the products.

If the substitutions are completed in time, the total release to surface water in $NP_{equiv.}$ at the downstream sites should decrease from 0.013 kg/a NP_{equiv} at the UK sunset date to cease at the end of the review period in-line with the delay due to the shelf life of the products. However, if the substitutions are delayed towards the end of the review period for all formulation activities, a maximum total annual release of 0.015 kg/a NP_{equiv} to surface water from all wide-dispersive uses could potentially be reached as a worst-case at the UK sunset date. Even though there is a certain risk of delay of substitution projects due to potential technical or regulatory difficulties and some delays have already occurred (see AoA), a delay of all projects until the end of the review period is highly unlikely.

Table 27. Expected and worst-case releases to surface water after STP and soil (from application of sewage sludge) per year in kg/a $NP_{equiv.}$ from 2022 until the end of 2027 considering RMMs implemented at the EU sunset date.

Use 3	Scenario	Unit	Downstream uses release to surface water	Downstream uses release to soil*
Release to surface water / soil after STP at sunset date (30th of June 2022)	**Expected release considering substitutions**	kg/a $NP_{equiv.}$	0.013	0.040
	Max total releases with delayed substitutions	kg/a $NP_{equiv.}$	0.015	0.046
Release to surface water / soil after STP at the end of review period (end of 2027)	**Expected release considering substitutions**	kg/a $NP_{equiv.}$	0.0031	0.009
	Max total releases with delayed substitutions	kg/a $NP_{equiv.}$	0.0071	0.022
Total release to surface water / soil after STP over the review period (2022-end of 2027)	**Expected release considering substitutions**	kg/5.5a $NP_{equiv.}$	0.0385	0.117
	Max total releases with delayed substitutions	kg/5.5a $NP_{equiv.}$	0.0568	0.173

* Releases to soil are worst-case as 100% of sludge is assumed to be applied to soil (see Section 9.3.2.1).

9.5.3. Results of the Monitoring Data and Validation of the 'Multifate' Model

A monitoring campaign was not performed for the use at downstream sites involving NPnEO addressed in this CSR, as a validated method to measure NPnEO or degradation products in wastewater at low concentrations was not available until recently (end of 2021). However, the same degradation mechanism for OPnEO and NPnEO can be assumed based on the general degradation mechanism that holds for all alkylphenol polyethoxylates according to [3] and [5]. Therefore, a validation of the model for OPnEO is also applicable for NPnEO. For these reasons, a monitoring campaign was conducted for OPnEO for the protein production processes covered in Use 4 of the EU dossier which served as a basis to validate the calculations made using the 'Multifate' model. The comparison of monitoring data with the modelled data confirmed that the assumptions used in the model 'Multifate' were very conservative (e.g. 100% of OPnEO released to wastewater; no complete mineralization), as the modelled concentrations were always by a factor of 30 to 440 higher compared to the measured data. Detailed data of this comparison are given in the CSR of Use 4 of the EU dossier in section 9.4.5. 'Results of the Monitoring Data and Validation of the 'Multifate' Model'[6].

NPnEO concentrations measured in liquid waste from IVD instruments are discussed in Section 9.3.1.1.

[6] Link to CSR of Use 4: https://echa.europa.eu/documents/10162/0775aa16-4c55-77b6-0d94-013c5ffae586

9.6. Potential Further RMMs at Downstream User Sites

In Section 9.3.1, the operational conditions for the use of assays containing OPnEO / NPnEO in laboratories / hospitals are described including a description of the different waste fractions generated. Taking already implemented RMMs into account, i.e. disposal of unused product as waste, ca. 84% OPnEO and 47% NPnEO of the total amounts used will be released via liquid waste (see mass balance for OPnEO and NPnEO in Sections 9.2.2.2 and 9.2.3.2, respectively). Releases of OPnEO and NPnEO to wastewater will be further reduced over the course of the review period by completed substitutions. They will reach zero at the latest at the end of the review period. In this section, it is discussed why further risk management measures to reduce emissions through liquid waste into wastewater during this transitional period is not technically and practically feasible. As considerations are the same for OPnEO and NPnEO, both substances are discussed together. Furthermore, this assessment focuses on the cobas® instruments used to perform CC / DM and HIV assays (see Table 8) as these are the main sources of release to wastewater at the UK sunset date. One other assay from which OPnEO is released to wastewater is RTD. RTD is not discussed separately as similar considerations as discussed below are also applicable for RTD. Please note that the situation described below is similar for laboratories, hospitals and blood banks. Therefore, when laboratories are mentioned, the information also refers to hospitals and blood banks. Note that the disposal of sewage sludge containing OPnEO / NPnEO on agricultural land is beyond the control of the applicant. Therefore, the implementation of further RMMs at this step is not possible.

Adaptation of the modules to selectively collect waste containing OPnEO or NPnEO

As discussed in Section 9.3.1, OPnEO / NPnEO are highly diluted in liquid waste from IVD instruments as concentrations in the assays are already low and are further diluted by liquid waste from other assays not containing these substances (+ rinsing water in case of mixing diluted and concentrated wastewater streams+ biological sample). The module set up could in theory therefore be adapted to collect only the waste containing OPnEO / NPnEO and other regulated substances. This would, however, imply the development of new IVD modules which would require the development of new hardware components and software by Roche's instrument partner. From Roche's side, such a change would require the in-house verification and validation of instrument function, the re-registration of the analyzer as new instrument in most countries including the UK as well as the re-registration of the entire IVD assay portfolio that is run on the instruments. The adaptation of the module set up would therefore be comparable to the development of a new analyzer generation that would require at least 5 years and may be further limited by development capacity at the instrument partner. [redacted] additional time is required to introduce the new instruments on the market taking obligations towards customers based on existing contracts into account. Therefore, it is estimated to take another 5-7 years until existing instruments would be replaced on the market. The total time of at least 10 years is considerably longer than the time planned for the substitutions. The additional cost for development is estimated to be more than [redacted] The cost does not yet take into account cost for replacing existing instruments on the market. Therefore, redevelopment of the instruments is not a feasible option to further reduce emissions.

Collection of all concentrated liquid waste from the instruments

As outlined above, separation of waste containing OPnEO / NPnEO is not a feasible option. Alternatively, it would in principle be possible to collect concentrated liquid waste separately from

diluted waste as the cobas® 6’000 and 8’000 modules and cobas® c 311 have separate outlets for these two waste fractions. cobas® e 411 is the only instrument with just one outlet.

The factors discussed below render collection of liquid waste disruptive for the operation of the laboratories or practically impossible. This is especially the case when such collection was not already planned during installation of the laboratory.

- Containers for concentrated waste are available to be integrated in the instruments for cobas® 6000 and 8000 modules. However, these containers are small in comparison to the volume of concentrated waste generated due to ergonomic reasons (containers must correspond to the health standards for the lifting of weights). For example, for cobas® 8’000 modules, a 5 L waste container is available, but at maximum throughput this volume of waste is generated within 2.5 hours. A large laboratory could have ca. 13 modules installed. The manual emptying of the containers up to every hour per module would be highly disruptive for the operation of such a large laboratory. It would therefore impact efficiency of the laboratory and potentially affect delivery of results for patients. Furthermore, it would not be possible to achieve throughput as required by the customer and specified by Roche in tenders. Finally, collection facilities would have to be available to store the wastewater for collection by a waste management company. This would not be possible in all laboratories due to space limitations (see considerations below).

- To avoid disruption of laboratory services as detailed above, instrument outlets for liquid waste could be directly connected to a larger waste container (e.g. 1’000 L tanks). Even though this may be possible in some cases, space is often limited in IVD laboratories. Similarly, outside of buildings space will not be readily available to install collection facilities and allow for collection by a waste management company. In addition, this would require additional tubing or even a new drainage system to connect instruments with the waste container. For a larger laboratory, up to two 1’000 L tanks (concentrated waste only) may be needed to allow for a weekly waste collection by a waste management company. As outlined in the SEA (Section 3.1.3), even modifications to buildings sometimes need to be made to house a new laboratory and which are then optimized with respect to the laboratory’s requirements and optimized for space (see Appendix 5). Facilities for liquid waste collection (i.e. containers and logistic facilities for the waste to be collected by a waste management company) are not foreseen during installation of laboratories, as this is not required by UK regulations (see Section 9.3.1.2 and Table 11 for common practices in the UK). Therefore, in many cases, modifications to the laboratory building, if possible, would be needed to allow for the collection of larger amounts of liquid waste. Consequently, several years are expected to be needed for such a modification in all laboratories. Cost can currently not be estimated but is expected to be very high considering necessary changes in laboratory buildings. In the UK, besides the high costs, space was identified as one of the main constraints for the installation of large waste containers. To illustrate this, space is so important that tenders may be lost to competitors in case of higher space requirements of Roche instruments. An example of a typical space situation in a UK laboratory can be found in SD5 (SD5_CSR_Laboratory_Space_Situation_RDL_Use 3_CONFIDENTIAL).

Incineration of collected liquid waste

Separate collection of concentrated liquid waste in laboratories where this was not already planned during installation of the laboratory is not considered feasible to be implemented within a reasonable timeframe and at reasonable cost as discussed above. Nonetheless, the theoretical consequences of incineration of the generated volume of liquid waste shall be discussed below.

It is estimated that 1'600 – 9'150 m^3 of concentrated liquid waste is generated by all cobas® 6000 / 8000 modules including cobas® c311 and e411 in the UK (see Appendix 1). In general, incineration facilities to incinerate this waste would likely be available throughout the UK. However, it is unclear if such incineration plants would accept the described liquid waste and if capacities for the generated volumes of waste of such low calorific value would be available (even though it is understood that in some cases incinerators will use this to address issues with high calorie wastes). Also, liquid waste may need to be transported to such facilities over considerable distances. Based on incineration cost in the UK (ca. 3'000 £ per ton), incineration would lead to total cost of ca. 4.8 to 27.6 mio £ per year. It has to be kept in mind that this waste is estimated to contain on average OPnEO at concentrations between 3.4 – 21.4 mg/L (0.1 – 50 mg/L) and NPnEO at concentrations between 0.005 – 0.3 mg/L (0.001 – 10 mg/L) (see Table 10).

The estimated energy demand in order to incinerate 1'600 – 9'150 m^3 of water is 4'181 – 23'908 GJ (based on simplified assumptions: Energy demand for heating the water from 15 °C to 100 °C for evaporation), which corresponds to CO_2 emissions of 232.3 – 1'328.2 t (assuming that the required energy is provided via natural gas). If low concentrated waste (only containing ca. 1% of released OPnEO and NPnEO) was additionally incinerated, amounts of up to 107'000 m^3 of water would need to be incinerated, requiring up to 279'580 GJ of energy, generating CO_2 emissions of up to 15'532 t (based on the above-mentioned assumptions). Additionally, CO_2 emissions from transport to incineration facilities would occur and were not considered in this calculation.

For all Benchmark® modules (for RTD assays) in the UK, the total liquid waste containing ca. [redacted] mg/L (5 – 30 mg/L) OPnEO, is estimated to be [redacted] m^3 (90 – 6'00 m^3). Based on incineration cost in the UK (ca. 3'000 £ per ton), this would lead to total cost of ca. [redacted] mio £ (0.27 to 1.8 mio £) per year. The estimated energy demand in order to incinerate [redacted] m^3 (90 – 600 m^3) of water is [redacted] GJ (235 – 1'568 GJ), which corresponds to CO_2 emissions of [redacted] t (13.1 – 87.1 t) based on the above-mentioned assumptions. Additionally, CO_2 emissions from transport to incineration facilities would occur and were not considered in this calculation.

This is unfavorable with respect to the energy needed for the incineration, and the overall reduction in impacts to the environment.

Pre-treatment of liquid waste before release to the sewer system

Alternative to collection and disposal of liquid waste, liquid waste could theoretically be pre-treated before release into the sewer system. Either collected waste could be treated or treatment could be performed with an online pre-treatment device. Collection of liquid waste was already discussed above. Therefore, this section focuses on online pre-treatment. However, considerations on pre-treatment methods similarly apply to collected waste.

Pre-treatment of liquid waste from analytical devices in laboratories before release to the sewer system is known to be common practice in some countries, e.g. in France. However, the pre-treatment is required not because of the possible presence of harmful chemicals in the waste, but because of obligatory disinfection of biological wastewater. Even though pre-treatment devices usually reduce chemical load in liquid waste in addition to treatment of biohazard, efficiency for removal of OPnEO / NPnEO by such treatment devices is not known and even generation of OP has been observed (see further discussion below). Even though, theoretically, similar devices could be installed in UK laboratories, this would therefore not be a feasible option to further reduce emissions.

In addition, the factors discussed below render such a procedure disruptive for the operation of the laboratories or practically impossible and would lead to additional costs.

Installation of pre-treatment devices

The installation of additional pre-treatment devices may not be feasible for existing modules due to space constraints at RDL's customers and the fact that the equipment is already set up in a way to use up as little space as possible. In this context similar considerations apply as for the installation of collection tanks discussed above. Even though pre-treatment devices are smaller than collection tanks, space requirements are still considerable. For example, common treatment devices in France are 525 x 435 x 340 mm (LxWxH) large, others are even larger (height >1m). Installment of such treatment devices in the existing laboratories as shown in SD5 (SD5_CSR_Laboratory_Space_Situation_RDL_Use 3_CONFIDENTIAL) would be difficult to achieve. In most cases such a module could not be installed adjacent to the instruments. This would require a lot of extra tubing to transport the water from the instruments to the pre-treatment module. This could lead to problems e.g. due to clogging of tubing and may require additional equipment such as pumps to transport the water to the treatment device. In the UK, space was identified as one of the main issues. As indicated above: space is so important that tenders may be lost to competitors in case of higher space requirements of Roche instruments. In addition, even if one treatment method was identified as suitable (see discussion below), such device would have to be available in sufficient quantities and the supplier would have to have capacities for installation of these devices. This would require a considerable amount of time and sufficient availability in the UK which is currently not expected. Furthermore, additional costs will arise due to the UK-wide installation of the pre-treatment modules. For example, modules currently available in France cost in the range of appr. 13'000 £ to 26'000 £. Several hundred of these modules would have to be installed if installation was possible in view of space constraints (see discussion above).

Efficacy of possible pre-treatment options

Currently, several pre-treatment devices are known. These pre-treatment methods were primarily designed for disinfection of biological wastewaters. Nevertheless, the treatment methods shall also lead to a reduction in the load of organic chemicals and could reduce concentrations of chemicals such as OPnEO and NPnEO. Therefore, the possible efficiency of selected commonly used methods was assessed regarding OPnEO / NPnEO removal. The known pre-treatment devices have not specifically been evaluated for OPnEO / NPnEO removal except for one case. However, similar methods (such as ozonation or other oxidation methods or activated carbon) have been evaluated for wastewater treatment for the removal of micropollutants, partially including OP or NP. Therefore, the general efficiency of these methods for OP(nEO) and NP(nEO) removal was researched in the literature (see Appendix 2).

In summary, available methods (see Appendix 2) will likely be able to degrade some of the OPnEO / NPnEO present in the liquid waste (especially regarding the fact that most treatment devices employ more than one method alone, e.g. a combination of electrolysis with subsequent UV), even though complete degradation is unlikely. Degradation highly depends on the composition of the liquid waste (which is very variable for IVD instruments), the method used and treatment time. In addition, under certain conditions, OP / NP (the critical degradation products of OPnEO / NPnEO) or other degradation products may be generated during treatment as has been shown for one treatment device. Therefore, an efficient method for removal of OPnEO / NPnEO in liquid waste from IVD instruments is currently not available. It will be difficult to identify a method or device having a high and reliable efficiency for complete OPnEO and NPnEO degradation for all kinds of IVD waste compositions. If

such a method or device was identified, the installation would require a large amount of time and would be associated with high cost (see above).

Cost for additional risk reduction measures

In general, the laboratory / hospital is responsible for waste disposal including the respective costs. However, if requirements for waste disposal were changed e.g. due to the presence of UK REACH Annex 14 substances in the reagents, laboratories / hospitals may expect RDL to cover the cost. The possible costs include costs for changes in the infrastructure where possible, incineration of liquid waste and / or purchasing in maintenance of treatment devices. Especially cost for reconstructions in a large number of laboratories could add up to a large sum of investment. If such costs cannot be claimed from Roche under the terms of a given contract, the customers - and thus ultimately insurance schemes and the healthcare system – would have to cover the additional cost.

Expected elimination of OPnEO and NPnEO by substitution

In the following, an overview of the ongoing OPnEO / NPnEO substitution projects with a focus on the products containing the largest amounts of OPnEO / NPnEO is given (see AoA for details on the substitution projects). It should be emphasized that in the past 6 years a large substitution effort has already been made and emissions of OPnEO / NPnEO have already been substantially reduced. For example, the number of assays containing OPnEO / NPnEO has already been reduced from 19 in 2019 (when the EU dossier was prepared) to 10 in the current dossier.

OPnEO

In the planning of substitution projects, assays with larger amounts employed were prioritized wherever possible.

The majority of OPnEO (>60%) is used in one assay (CC3). When the EU dossier was submitted, the expected time of substitution in the formulation for the product CC3 was expected to be end of 2019. However, technical difficulties have occurred. Current feasibility tests are promising and if these tests and the subsequent performance verification are successful, substitution will be completed by end 2023. After this date, releases from laboratories from stocks of this assay with OPnEO will go down and at a maximum 1.5 years (duration of shelf life) later, i.e. 3 years after the UK sunset date, releases will have completely ceased unless further technical difficulties are encountered (see AoA for further details).

Based on the current status of the substitution projects, releases from the majority of the remaining OPnEO usage (<40%) is expected to have ceased earlier or with a similar timeline.

NPnEO

The amount of NPnEO used by the UK sunset date is already very small, i.e. with 0.39 kg/a, less than 1 kg/a. This amount will be further reduced in the course of the review period and eliminated by the end of the review period due to replacement of the instruments by a new generation working with a NPnEO-free assay.

Conclusion

Based on the above considerations, implementation of further RMMs at laboratory level are not considered technically and practically feasible. On the one hand suitable methods to eliminate OPnEO

/ NPnEO at the low concentrations present in liquid waste are not available. Incineration would require large amounts of energy and thus lead to high CO_2 emissions and high cost. Furthermore, adaptation of laboratory installations to collect or treat the large amounts of wastewater would be a major logistic challenge and require reconstruction or modifications of buildings in many cases. Therefore, the implementation of any kind of waste disposal/treatment – if at all possible in all laboratories – would take considerable time. Consequently, these measures would only become effective at a time when the majority of emissions is already eliminated or will be eliminated in the near future due to completed substitutions. In addition, redevelopment and installation of instruments to selectively collect or treat OPnEO / NPnEO-containing waste would take longer than the completion of all substitutions (longer than review period). Therefore, substitution of OPnEO and NPnEO in the reagents as fast as possible is considered the only option to further reduce the emissions and to completely eliminate them latest by the end of the review period.

10. EXPOSURE ASSESSMENT RELATED TO COMBINED EXPOSURE AND COMPARISON WITH AVAILABLE REFERENCE VALUES

10.1. Exposure Assessment Related to Combined Exposure and Comparison with Available Reference Values – OPnEO

- ⇨ **RMMs to minimise releases have been implemented** as far as technically and practically feasible. **Releases will be continuously reduced by substitution**.
- ⇨ Total release to surface water (after STP) of **$OP_{equiv.}$ is 6.22 kg/a**. Release of **$OP_{equiv.}$** to agricultural soil after STP is 5.19 kg/a.
- ⇨ Indicative calculation of remaining risk: Predicted environmental concentrations (PEC) for OP in surface water and soil/sediment were usually **below the available reference values (EQS and PNEC)** for regional and combined exposure.

10.1.1. Overview of the Uses Applied For and their Interrelation

As already mentioned, the current exposure assessment was generated to support RDL's applications for authorisation for the following use:

- Use 3: Use of Octyl- and Nonylphenolethoxylates in *in vitro* diagnostic (IVD) assays specified in Appendix 1 to the AoA.

This use covers the downstream uses at hospitals / laboratories.

For the purpose of the exposure assessment, the combined local release per site and combined regional release across uses must be estimated independent of the use applied for. Therefore, an overview of the activities involving OPnEO currently falling in the scope of the AfA of RDL is provided for the downstream users' sites i.e. at hospitals / laboratories in Figure 10, which depicts the on-site activities for Use 3.

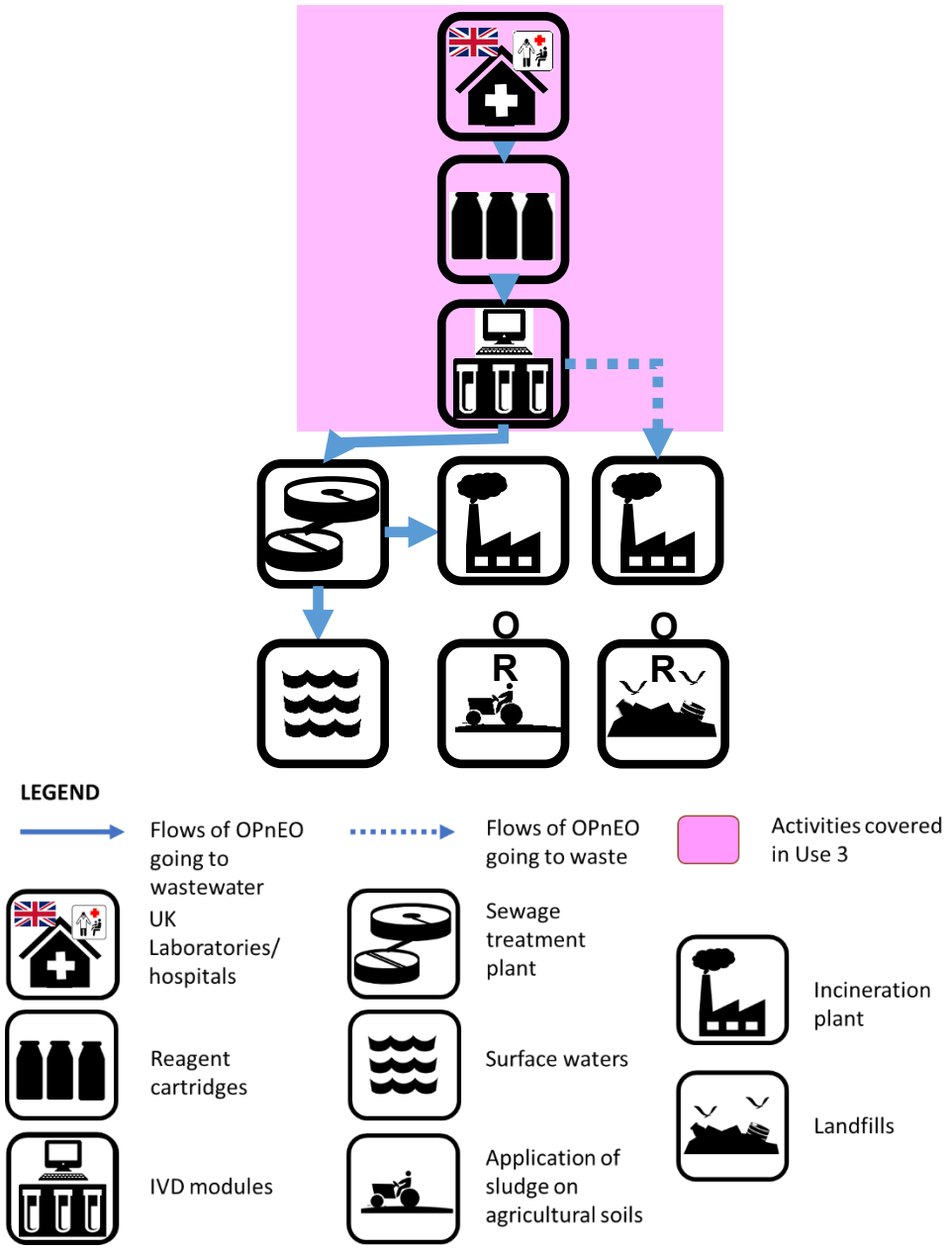

Figure 10. Overview of the activities involving OPnEO falling in scope of Use 3 performed at the downstream users' sites i.e. at hospitals / laboratories.

The IVD assays covered in this AfA run on IVD modules installed in hospitals or laboratories. From some instruments, waste of used reagents and test samples are collected at hospitals / laboratories and disposed of as solid waste. As RMM for all assays implemented since the EU sunset date (the 4th of January 2021), waste of unused product is collected and disposed of as solid waste. The remaining OPnEO is released to the sewer system with liquid waste from the instruments (see details in Section 9.3.1 and 9.3.2.2 of this CSR). It is not technically and practically feasible to implement further RMMs (see Section 9.6 of this CSR). However, releases will be continuously reduced by substitution (see Section 9.4.2 of this CSR).

The combined exposure assessment presented in the following sections comprises:

- The total releases from all wide-dispersive activities involving OPnEO (see Section 10.1.2.1.1.1) as well as total predicted local exposure concentrations resulting from these releases (see Section 10.1.2.1.2).
- The total regional predicted exposure concentrations considering the activities involving OPnEO of all wide-dispersive activities expected in the region (see Section 10.1.2.1.1.2).
- The total predicted local exposure concentrations considering all wide-dispersive uses (combined exposure, see Section 10.1.2.1.2).
- A comparison of the combined exposure with available measurements in STP effluents, background concentrations in surface water and available reference values (see Section 10.1.2.1.3).

10.1.2. Environment (Combined for All Emission Sources)

10.1.2.1. Environment

10.1.2.1.1. All Uses (Regional Scale)

10.1.2.1.1.1. Total Releases

Table 28. Total releases to environmental compartments after STP per year from all life cycle stages in kg/a $OP_{equiv.}$ at the end of 2027 (worst-case).

Use 3	**Unit**	**Wide-dispersive uses**	**Waste**	**Total releases after STP per year**
		Laboratories / hospitals		**TOTAL**
SURFACE WATER	kg/a $OP_{equiv.}$	6.22	$1.74 \cdot 10^{-5}$	**6.22**
SOIL	kg/a $OP_{equiv.}$	5.19	Landfill: via STP (sludge): $1.45 \cdot 10^{-5}$ Direct release to soil: 0.00476	**5.19**
AIR	kg/a $OP_{equiv.}$	$1.53 \cdot 10^{-7}$	$8.72 \cdot 10^{-11}$	**$1.53 \cdot 10^{-7}$**

Remarks:

The yearly releases at the end of 2027 to surface water and soil are worst-case as all substitutions are assumed to be delayed. In addition, 100% of sludge is assumed to be applied to soil for Use 3. The worst-case assumes maximum yearly release to increase over time due to sales development if all substitutions were delayed until the end of the review period, which is, however, unlikely. Maximum total release of $OP_{equiv.}$ to surface water and soil over the course of the review period for the use covered in this CSR is given in Table 21.

10.1.2.1.1.2. Regional Exposure

The predicted regional environmental concentrations listed in Table 29 were calculated with the 'Multifate' model based on the wide-dispersive uses covered in this CSR under the assumption that 100% of the total amount are released in the region [12].

Table 29. Predicted regional environmental concentrations in $OP_{equiv.}$

Protection target \ PEC regional	Unit	PEC regional
Freshwater	µg/L	$6.19 \cdot 10^{-6}$
Sediment (freshwater)	mg/kg	$4.88 \cdot 10^{-7}$
Marine water	µg/L	$6.26 \cdot 10^{-6}$
Sediment (marine water)	mg/kg	$2.26 \cdot 10^{-7}$
Agricultural soil	mg/kg	$9.02 \cdot 10^{-7}$
Soil porewater / groundwater	pg/L	0.0094
Air	pg/m^3	$2.60 \cdot 10^{-8}$

Remarks on measured regional concentrations:

Regional concentrations of OPnEO were not measured specifically for the purpose of the present CSR. However, environmental background concentrations are available (see Section 10.1.2.1.3 for more details).

Remarks on risk characterisation for regional concentrations:

Risk characterisation was not assessed because no threshold can be derived for the endpoint 'endocrine disruptors properties of the degradation products' for the substance. Instead, risk and exposure minimisation are demonstrated in this CSR. The PECs regional are compared with Environmental Quality Standards as an indication of remaining risk in Section 10.1.2.1.3.

10.1.2.1.2. Local Exposure Due to All Wide-Dispersive Uses

Table 30. Exposure and risk due to all wide-dispersive uses in $OP_{equiv.}$

Protection target \ PEC local	Unit	Use 3 local	Use 3 local waste	Regional	TOTAL
Sewage treatment plant (effluent)	µg/L	0.0597	$2.38 \cdot 10^{-5}$	not applicable	**0.0597**
Freshwater	µg/L	0.00597	$2.38 \cdot 10^{-6}$	$6.19 \cdot 10^{-6}$	**0.00597**
Sediment (freshwater)	mg/kg	0.000145	$5.79 \cdot 10^{-8}$	$4.88 \cdot 10^{-7}$	**0.000145**
Marine water	µg/L	0.000597	$2.38 \cdot 10^{-7}$	$6.26 \cdot 10^{-6}$	**0.000603**
Sediment (marine water)	mg/kg	0.0000145	$5.79 \cdot 10^{-9}$	$2.26 \cdot 10^{-7}$	**0.0000147**
Agricultural soil	mg/kg	0.0000458	$1.69 \cdot 10^{-8}$	$9.02 \cdot 10^{-7}$	**0.0000467**
Soil porewater / groundwater	pg/L	not applicable	0.044	0.0094	**0.0534**
Air	pg/m^3	0.000167	$6.64 \cdot 10^{-8}$	$2.60 \cdot 10^{-8}$	**0.000167**

Remarks:

Risk characterisation was not assessed because no threshold can be derived for the endpoint ‘endocrine disruptors properties of the degradation products’ for the substance. Instead, risk and exposure minimisation are demonstrated in this CSR. PEC per site are compared with EQS / PNEC as an indication of remaining risk in Section 10.1.2.1.3.

10.1.2.1.3. Comparison of Combined Exposure With Available Measurements at STP, Background Concentrations and Available Reference Values

10.1.2.1.3.1. Comparison of Combined Exposure With Available Background Concentrations and Available Reference Values

Any comparisons of modelled / measured concentrations with EQS / PNEC (predicted no-effect concentration) values in this section are for illustration purposes only since for this risk assessment, we assume that no threshold value can be assigned to the endocrine disrupting substances covered in this AfA (e.g., [1]).

Wide-dispersive uses

The combined freshwater PEC for wide-dispersive uses was calculated to be 0.00597 µg/L for an average size-laboratory to 0.000225 µg/L for a big laboratory, i.e. 5.97 ng/L to 0.225 ng/L (Use 3 + regional; $OP_{equiv.}$; see Table 31), respectively. This concentration is lower than measured environmental concentrations (rivers and groundwaters across the EU and the UK in the range of 20-700 ng/L (see Table 8, Table 31). In reality, the relative contribution of wide-dispersive uses (as quantified and described below) to OP concentrations in surface waters will be lower than the values depicted in Table 31 as the modelled PEC values are $OP_{equiv.}$ (i.e. the sum of OP and all of its precursors) and the measured concentrations are OP concentrations only. Despite these conservative assumptions, the comparison of modelled $OP_{equiv.}$ with measured OP concentrations already shows

that the wide-dispersive PEC is smaller than the measured values. Hence, contribution of wide-dispersive uses as covered in this CSR to the OP that is already present is small.

Local $OP_{equiv.}$ in soil porewater of 0.044 pg/L, i.e. 0.000000044 µg/L (which, according to the guidance document, are assumed to be identical to groundwater concentrations) are by a factor of 100'000 lower than calculated surface water concentrations of 0.00597 µg/L due to wide-dispersive uses and hence, are not assumed to contribute to $OP_{equiv.}$ in surface water (Table 30).

The local PEC for wide-dispersive uses in surface water (0.225 – 5.97 ng/L, see above) is also approx. 16 – 440 times lower than the AA-EQS of 100 ng/L for OP, resulting in a PEC / EQS ratio of $6 \cdot 10^{-5}$ – 0.06 (Table 31). Furthermore, the local PEC for wide-dispersive uses in surface water is also approx. 5 times lower than the PNEC of 34 ng/L for OP, resulting in a PEC / PNEC ratio of 0.18 (see Table 31). Since the modelling assumptions were demonstrated to be very conservative (CSR of Use 4 of the EU dossier in section 9.4.5. 'Results of the Monitoring Data and Validation of the 'Multifate' Model'[7]), it can be assumed that the 'true' contribution of wide-dispersive uses to environmental OP concentrations will likely be much lower than the EQS / PNEC value.

Regional exposure

Total local exposure is calculated by summing up exposure from local uses and regional exposure for each site. The contribution of regional and local exposures to combined local exposure were evaluated by comparing the respective predicted environmental concentrations for each site as depicted below. In summary, the respective local sources contributed to a greater extent than regional exposure to total exposure of surface waters with $OP_{equiv.}$ for local wide-dispersive use.

Regional $OP_{equiv.}$ in soil porewater (which, according to the guidance document, are assumed to be identical to groundwater concentrations) are by a factor of approx. 650 lower than calculated surface water concentrations and hence, are not assumed to contribute to $OP_{equiv.}$ in surface water (Table 29).

Table 31. Comparison of combined local and regional PECs (in $OP_{equiv.}$) with available background and reference values for fresh waters.

Sites / Region	Combined Freshwater PEC [µg/L]	Background values [µg/L]	EQS [µg/L]	PNEC** [µg/L]	Ratio PEC/EQS	Ratio PEC/PNEC
Average-size laboratory	0.00597	0.02-0.7*	0.1	0.034	0.060	0.18
Big laboratory	0.000225	0.02-0.7[1]	0.1	0.034	0.0023	0.0066
Regional	$6.19 \cdot 10^{-6}$	0.02-0.7[1]	0.1	0.034	$6.2 \cdot 10^{-5}$	0.00018

* range of surface and groundwaters, see Table 15

** PNEC value as determined in the hazard assessment of this CSR ('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, Patricia Janz, Christiane Brandt). See supporting document to the CSR 'SD1_CSR_Hazard_assessment_OPnEO_RDL_Use3'.

[7] Link to CSR of Use 4: https://echa.europa.eu/documents/10162/0775aa16-4c55-77b6-0d94-013c5ffae586

All PECs were calculated based on worst-case releases at the end of 2027, i.e. assuming that all substitutions are delayed until the end of the review period.

Comparison of combined local and regional PECs (in $OP_{equiv.}$) with available reference values for sediment and soil

Comparison of combined local and regional PECs with available reference values for sediment (freshwater as well as marine sediment) and soil (Table 32) shows that for all of the assessed sites/regions and compartments, $OP_{equiv.}$ are lower than the respective derived PNEC values (Ratio PEC / PNEC <1).

Table 32. Comparison of combined local and regional PECs (in $OP_{equiv.}$) with available reference values for sediment and soil.

Compartment	Site / Region	Combined PEC (mg/kg)	PNEC* (mg/kg)	Ratio PEC / PNEC
Sediment (freshwater)				
	Wide-dispersive uses	0.000145	0.028	**0.0052**
	Regional	$4.88 \cdot 10^{-6}$	0.028	**0.00017**
Sediment (marine)				
	Wide-dispersive uses	$1.45 \cdot 10^{-5}$	0.0028	**0.0052**
	Regional	$2.26 \cdot 10^{-7}$	0.0028	**0.000081**
Agricultural soil				
	Wide-dispersive uses	$4.58 \cdot 10^{-5}$	0.0056	**0.0082**
	Regional	$9.02 \cdot 10^{-7}$	0.0056	**0.00016**

* PNEC values as determined in the hazard assessment of this CSR ('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, Patricia Janz, Christiane Brandt). See supporting document to the CSR 'SD1_CSR_Hazard_assessment_OPnEO_RDL_Use3'.

10.1.2.2. Man via the Environment

Not required

10.1.3. Human Health (Related to Combined Exposure)

10.1.3.1. Workers

Not required

10.1.3.2. Consumers

Not required

10.2. Exposure Assessment and Indicative Risk Characterisation Related to Combined Exposure – NPnEO

- ⇨ **RMMs to minimise releases have been implemented** as far as technically and practically feasible. **Releases will be continuously reduced by substitution**.
- ⇨ Total release to surface water (after STP) of **$NP_{equiv.}$ is 0.015 kg/a.** Release of $NP_{equiv.}$ to agricultural soil after STP is 0.046 kg/a.
- ⇨ Indicative calculation of remaining risk: Predicted environmental concentrations (PEC) for $NP_{equiv.}$ in surface water and soil/sediment were usually **below the available reference values (EQS and PNEC)** for NP for regional and combined exposure.

10.2.1. Overview of the Used Applied For and Their Interrelation

As already mentioned, the current exposure assessment was generated to support RDL's applications for authorisation for the two following use of NPnEO:

- Use 3: Use of Octyl- and Nonylphenolethoxylates in *in vitro* diagnostic (IVD) assays specified in Appendix 1 to the AoA.

For the purpose of the exposure assessment, the combined local release per site and combined regional release across uses must be estimated independent of the use applied for. Therefore, an overview of the activities involving NPnEO currently falling in the scope of the AfA of RDL is provided for the downstream users' sites i.e. at hospitals / laboratories in Figure 11, which depicts the on-site activities at the downstream use taking place at hospitals / laboratories / blood banks in scope of Use 3.

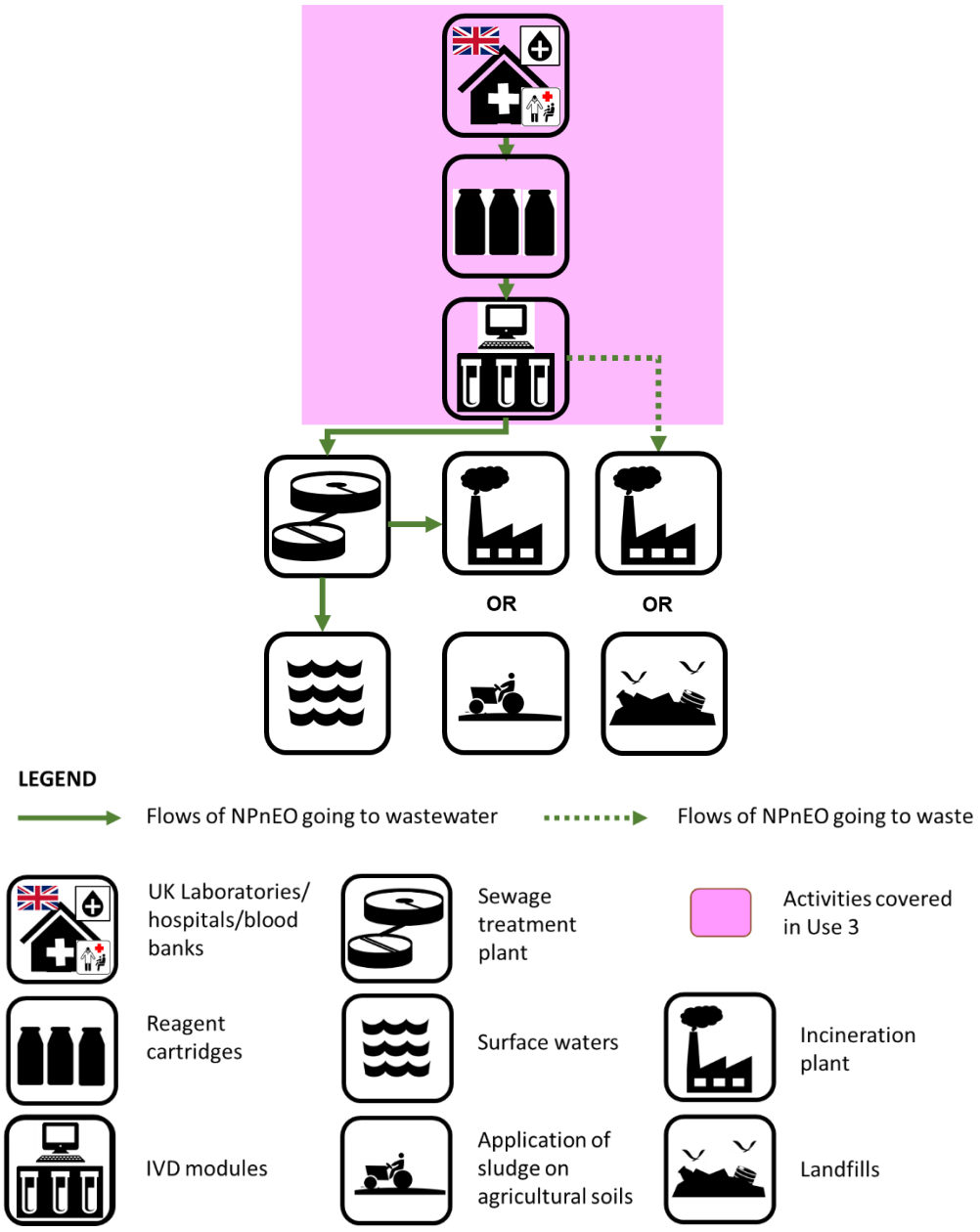

Figure 11. Overview of the activities involving NPnEO falling in scope of Use 3 performed at the downstream users 'sites i.e. at hospitals / laboratories / blood banks.

The IVD assays covered in this AfA run on IVD modules, installed in hospitals or laboratories and blood banks. From some instruments, waste of used reagents and test samples are collected at laboratories, hospitals and/or blood banks and disposed of as solid waste. As RMM for all assays implemented since the EU sunset date (the 4th of January 2021), waste of unused product is collected and disposed of as solid waste. The remaining NPnEO is released to the sewer system with liquid waste from the instruments (see details in Section 9.3.1 and 9.3.2.2 of this CSR). It is not technically and practically feasible to implement further RMMs (see Section 9.6 of this CSR). However, releases will be continuously reduced by substitution (see Section 9.5.2 of this CSR).

The combined exposure assessment presented in the following sections comprises:

- The total releases from wide-dispersive activities involving NPnEO (see Section 10.2.2.1.1.1).
- The total regional predicted exposure concentrations considering the activities involving NPnEO of all wide-dispersive activities expected in the region (see Section 10.2.2.1.1.2).
- The total predicted local exposure concentrations considering all wide-dispersive uses (combined exposure, see Section 10.2.2.1.2).
- A comparison of the combined exposure with available measurements at STP, background concentrations and available reference values (see Section 10.2.2.1.3).

10.2.2. Environment (Combined for All Emission Sources)

10.2.2.1. Environment

10.2.2.1.1. All Uses (Regional Scale)

10.2.2.1.1.1. Total Releases

Table 33. Total releases to surface water after STP per year from all life cycle stages in kg/a $NP_{equiv.}$ at sunset date.

Use 3		**Wide-dispersive uses**	**Waste**	**Total releases after STP per year**
	Unit	**Laboratories / hospitals**		**TOTAL**
SURFACE WATER	kg/a $NP_{equiv.}$	0.015	$2.00 \cdot 10^{-7}$	**0.015**
SOIL	kg/a $NP_{equiv.}$	0.046	Landfill: via STP (sludge): $4.46 \cdot 10^{-7}$ Direct release to soil: 0.0003	**0.046**
AIR	kg/a $NP_{equiv.}$	$4.91 \cdot 10^{-7}$	$6.56 \cdot 10^{-12}$	**$4.91 \cdot 10^{-7}$**

Remarks:

The yearly releases at the sunset date to surface water and soil are worst-case as all substitutions are assumed to be delayed. In addition, 100% of sludge is assumed to be applied to soil. Total maximum

release of $NP_{equiv.}$ to surface water and soil over the course of the review period for the use covered in this CSR is given in Table 33.

10.2.2.1.1.2. Regional Exposure

The predicted regional environmental concentrations listed in Table 34 were calculated with the 'Multifate' model based on the wide-dispersive uses covered in the CSR of Use 3 under the assumption that 100% of the total amount are released in the region [12].

Table 34. Predicted regional environmental concentrations in $NP_{equiv.}$

Protection target\ PEC regional	Unit	PEC regional
Freshwater	µg/L	$5.27 \cdot 10^{-11}$
Sediment (freshwater)	mg/kg	$1.41 \cdot 10^{-11}$
Marine water	µg/L	$1.90 \cdot 10^{-7}$
Sediment (marine water)	mg/kg	$1.76 \cdot 10^{-6}$
Agricultural soil	mg/kg	$1.53 \cdot 10^{-10}$
Soil porewater / groundwater	pg/L	$0.553 \cdot 10^{-6}$
Air	pg/m^3	$1.04 \cdot 10^{-12}$

Remarks on measured regional concentrations:

Regional concentrations of NPnEO were not measured specifically for the purpose of the present CSR. However, environmental background concentrations are available (see Section 10.2.2.1.3 for more details).

Remarks on risk characterisation for regional concentrations:

Risk characterisation was not assessed because no threshold can be derived for the endpoint 'endocrine disruptors properties of the degradation products' for the substance. Instead, risk and exposure minimisation are demonstrated in this CSR. The PECs regional are compared with Environmental Quality Standards as an indication of remaining risk in Section 10.2.2.1.3.

10.2.2.1.2. Local Exposure Due to All Wide-Dispersive Uses

Table 35. Exposure and risk due to all wide-dispersive uses in $NP_{equiv.}$

Protection target\ PEC local	Unit	Use 3 local	Use 3 local waste	Regional	TOTAL
Sewage treatment plant (effluent)	µg/L	$4.76 \cdot 10^{-4}$	$2.74 \cdot 10^{-7}$	not applicable	**$4.76 \cdot 10^{-4}$**
Freshwater	µg/L	$4.76 \cdot 10^{-5}$	$2.74 \cdot 10^{-8}$	$5.27 \cdot 10^{-11}$	**$4.76 \cdot 10^{-5}$**
Sediment (freshwater)	mg/kg	$3.87 \cdot 10^{-6}$	$2.23 \cdot 10^{-9}$	$1.41 \cdot 10^{-11}$	**$3.87 \cdot 10^{-6}$**
Marine water	µg/L	$4.76 \cdot 10^{-6}$	$2.74 \cdot 10^{-9}$	$1.90 \cdot 10^{-7}$	**$4.95 \cdot 10^{-6}$**

Protection target\ PEC local	Unit	Use 3 local	Use 3 local waste	Regional	TOTAL
Sediment (marine water)	mg/kg	$3.87 \cdot 10^{-7}$	$2.23 \cdot 10^{-10}$	$1.76 \cdot 10^{-6}$	**$2.15 \cdot 10^{-6}$**
Agricultural soil	mg/kg	$8.24 \cdot 10^{-7}$	$4.72 \cdot 10^{-10}$	$1.53 \cdot 10^{-10}$	**$8.24 \cdot 10^{-7}$**
Soil porewater / groundwater	pg/L	not applicable	0.063	$5.53 \cdot 10^{-7}$	**0.063**
Air	pg/m^3	$18.67 \cdot 10^{-6}$	$4.99 \cdot 10^{-9}$	$2.60 \cdot 10^{-10}$	**$18.67 \cdot 10^{-6}$**

Remarks:

Risk characterisation was not assessed because no threshold can be derived for the endpoint ‘endocrine disruptors properties of the degradation products’ for the substance. Instead, risk and exposure minimisation are demonstrated in this CSR. PECs per site are compared with EQS as an indication of remaining risk in Section 10.1.2.1.3.

10.2.2.1.3. Comparison of Combined Exposure with Available Measurements at STP, Background Concentrations and Available Reference Values

10.2.2.1.3.1. Comparison of Combined Exposure with Available Background Concentrations and Reference Values

Any comparisons of modelled / measured concentrations with EQS / PNEC (predicted no-effect concentration) values in this section are for illustration purposes only since for this risk assessment, we assume that no threshold value can be assigned to the endocrine disrupting substances covered in this AfA (e.g., [1]).

Wide-dispersive uses

The local PEC in surface water for wide-dispersive uses was calculated to be 0.0000476 µg/L for an average size laboratory and 0.00175 µg/L for a big blood bank, i.e. 0.0476 – 1.75 ng/L (Use 3 + regional; $NP_{equiv.}$; Table 36). These concentrations are a factor of 30 – 2’100 lower than the measured concentration of NP in surface waters of 50 – 100 ng/L (Table 36). In reality, the relative contribution of wide-dispersive uses (as quantified and described below) to NP concentrations in surface waters will be lower than the values depicted below as the modelled PEC values are $NP_{equiv.}$ (i.e. the sum of NP and all of its precursors) and the measured concentrations are NP concentrations only. Despite these conservative assumptions, the comparison of modelled $NP_{equiv.}$ with measured NP concentrations already shows that the wide-dispersive PEC is smaller than the measured values. Hence, contribution of wide-dispersive uses as covered in this CSR to the NP that is already present is small.

Local $NP_{equiv.}$ in soil porewater of 0.063 pg/L, i.e. 0.000000063 µg/L (which, according to the guidance document, are assumed to be identical to groundwater concentrations) are by orders of magnitude lower than calculated surface water concentrations of 0.0000476 µg/L due to wide-dispersive uses and hence, are not assumed to contribute to $NP_{equiv.}$ in surface water (Table 36).

The local PEC for wide-dispersive uses in surface water (0.476 – 1.75 ng/L, see above) is also approx. 25 – 90 times lower than the AA-EQS of 43 ng/L for NP, resulting in a PEC / EQS ratio of 0.0011 – 0.041 (Table 36). Since the modelling assumptions were demonstrated to be very conservative (CSR of Use 4 of the EU dossier in section 9.4.5. ‘Results of the Monitoring Data and Validation of the

'Multifate' Model'[8]), it can be assumed that the 'true' contribution of wide-dispersive uses to environmental NP concentrations will likely be much lower than the EQS value.

Regional exposure

Total local exposure is calculated by summing up exposure from local uses and regional exposure for each site. The contribution of regional and local exposures to total local exposure were evaluated by comparing the respective predicted environmental concentrations for each site as depicted below. In summary, the respective local sources contributed to a greater extent than regional exposure to total exposure of surface waters with $NP_{equiv.}$.

Table 36. Comparison of combined local and regional PECs (in $NP_{equiv.}$) with available reference values for fresh waters

Sites/Region	Unit	Combined Freshwater PEC [µg/L]	Background values (range)* [µg/L]	EQS [µg/L]	Ratio PEC / EQS
Wide-dispersive uses					
Average-size laboratory	µg/L	$4.76 \cdot 10^{-5}$	0.05-0.1	0.043	0.0011
Big blood bank	µg/L	$1.75 \cdot 10^{-3}$	0.05-0.1	0.043	0.041
Regional	µg/L	$5.27 \cdot 10^{-11}$	0.05-0.1	0.043	$1.22 \cdot 10^{-9}$

* Range of surface and groundwaters, see Table 10

Comparison of combined local and regional PECs (in $NP_{equiv.}$) with available reference values for sediment and soil.

No reference values for sediment and soil were available for NP.

10.2.2.2. Man via the Environment

Not required

10.2.3. Human Health (Related to Combined Exposure)

10.2.4. Workers

Not required

10.2.5. Consumers

Not required

[8] Link to CSR of Use 4: https://echa.europa.eu/documents/10162/0775aa16-4c55-77b6-0d94-013c5ffae586

10.3. Conclusions

RMMs to minimise releases of OPnEO and NPnEO to wastewater as far as technically and practically feasible have been in place since the EU sunset date (the 4th of January 2021). These RMMs include disposal of unused reagents in cartridges as waste at laboratories / hospitals. Emissions will be further reduced by completion of substitution projects over the course of the review period and will be fully eliminated by the end of the review period. Implementation of further RMMs is not considered technically and practically feasible. The risks related to the continued use of OPnEO and NPnEO can thus be considered as minimised. In total, yearly releases to surface water will be 7.61 kg/a $OP_{equiv.}$ and 0.015 kg/a $NP_{equiv.}$ as a maximum. Yearly releases to soil via application of sludge will be 6.35 kg/a $OP_{equiv.}$ and 0.046 kg/a $NP_{equiv.}$ as a maximum. For $NP_{equiv.}$ these maximum releases will be reached at the UK sunset date. For $OP_{equiv.}$these maximum releases could be reached until the end of the review period as a worst-case.

11.REFERENCES

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APPENDIXES

Appendix 1

To CSR Use 3

Assessment per instrument – amount of liquid waste

Assessment per instrument - amount of liquid waste

	Information on generated waste per instrument and waste handling from Instructions of Use		Amount of waste per hour				Operating time				Amount of waste per year per module				Number of modules installed in UK	Amount of waste per year TOTAL UK				Amount of waste per year TOTAL UK			
			High concentrated liquid waste		Low concentrated liquid waste		Operating hours per day		Operating days		High concentrated liquid waste per year		Low concentrated liquid waste per year			High concentrated liquid waste per year		Low concentrated liquid waste per year		High concentrated liquid waste per year		Low concentrated liquid waste per year	
			L/h	L/h	L/h	L/h	h/day	h/day	days / year	days / year	L/year	L/year	L/year	L/year		L/year	L/year	L/year	L/year	m3/year	m3/year	m3/year	m3/year
			min	Max	min	max	min	max	min	max	min	Max	min	Max		min	max	min	max	min	max	min	max
	Type of liquid waste at each outlet (concentrated / diluted / mixed outlet)	**Outlet to which the liquid from the different reagents (R1, R2, …) is going**																					
RTD:																							
BenchMark	Outlet 1: Diluted waste	Outlet 1: Diluted waste	0	0	0.37	0.37	12	12	255	360	0	0	1'132	1'598									
CC/DM:																							
Integra 400+	Outlet 1: Concentrated and diluted waste	Outlet 1 : R1+R2	0	0	1.3	1.3	5	8	255	360	0	0	1'658	3'744									
cobas 6000*	Outlet 1: concentrated waste Outlet 2: diluted waste	Outlet 1: concentrated waste	1.125	2.25	5.4	10.8	8	24	255	360	2'295	19'440	11'016	93'312									
cobas 8000**	Outlet 1: concentrated waste Outlet 2: diluted waste	Outlet 1: concentrated waste	1.02	2.04	15	30	8	24	255	360	2'081	17'626	30'600	259'200									
cobas c 311	Outlet 1 : concentrated (tSE Waste only) Outlet 2: diluted waste	Outlet 2 : Dilutetd waste	0.325	0.65	5.6	11.2	5	8	255	360	414	1'872	7'140	32'256									
cobas c 111	Outlet 1 : concentrated and diluted	Outlet 1 : 100%	0.17	0.34	0	0	4	8	255	360	0	0	0	0									
HIV:																							
cobas e 411	Outlet 1: Diluted and concentrated Material comes together. The Waste is very diluted.	Only one Outlet for Liquid Waste	0.45	0.9	0	0	5	12	255	360	574	3'888	0	0									
cobas 6000 cobas e 601	Outlet 1: concentrated waste Outlet 2: diluted waste	Outlet 1: concentrated waste and disposable waste	0.45	0.9	9	18	8	16	255	360	918	5'184	18'360	103'680									
cobas 8000 cobas e 602	Outlet 1: concentrated waste Outlet 2: diluted waste	Outlet 1: concentrated waste and disposable waste	0.5	1	9.5	19	8	16	255	360	1'020	5'760	19'380	109'440									
CC/DM total																**1'141'425**	**7'134'696**	**11'586'741**	**69'705'306**	**1'141**	**7'135**	**11'587**	**69'705**
HIV total																**449'578**	**1'997'892**	**6'610'620**	**27'997'920**	**450**	**1'998**	**6'611**	**27'998**
TOTAL																				**1'591**	**9'133**	**18'197**	**97'703**

***cobas 6000: Various combinations of modules c501/502 together with Elecsys® modules**

****cobas 8000: Various combinations of modules c701/702 together with Elecsys® modules**

Appendix 2

To CSR Use 3

Pre-treatment of liquid waste before release to the sewer system

Pre-treatment of liquid waste before release to the sewer system

Efficiency of additional pre-treatment devices in the laboratories

The possible efficiency towards OPnEO / NPnEO removal of selected commonly used pre-treatment methods in France was evaluated. Such data for pretreatment devices is very limited. However, similar methods (such as ozonation or other oxidation methods or activated carbon) have been evaluated for wastewater treatment for the removal of micropollutants, partially including OP or NP. Therefore, general efficiency of these methods for OP(nEO) and NP(nEO) removal was checked in the literature (Table 1)

Table 1. Efficiency towards OPnEO / NPnEO removal (literature data) of treatment methods employed in liquid wastewater pre-treatment devices in the laboratories

Method	Performance of method towards OPnEO/NPnEO and degradation products (literature data)
Ozonation	Approximately 90% of NP removed from STP effluents [2][1] 20-70% of OP removed from STP effluents[2] Efficiency 10-70% for NP and -100-40% for OP (negative removal = generation of OP from OPnEO)[3] NP was degraded efficiently, however, much lower effectiveness for NP1EO decomposition [3] Almost complete destruction of OPnEO / NPnEO (with exception of Triton X-705) represented by decay of UV absorption, however, increase of bacterial growth inhibition (1.5 to 4 times increase in toxicity) [4] 54% NPnEO degradation under optimized laboratory degradation conditions, however, from the study no definite conclusion can be drawn whether degradation was complete or initial; additionally: competition from natural organic matters in river water samples [5]
UV	The percent relative inhibition towards Vibrio fischeri increased from 9% to 33% after 120 min-UV-C treatment. Unidentified oxidation products were the most likely origin of the acute toxicity in UV-C photolysis [6]. Toxic 4-nonylphenol was never found as a byproduct of the degradation after any of the treatments [7]. At a maximum UV irradiation, 50% of OP were degraded in ca. 15 min. The presence of humic acid in the reaction solution caused a decrease in

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[2] Untersuchungen zur Eliminierung gefährlicher Stoffe, Landesamt für Umwelt, Landwirtschaft und Geologie, Freistaat Sachsen, https://www.umwelt.sachsen.de/umwelt/wasser/download/120830_Schlussbericht_lfulg_spurenstoffe__endfassung.pdf

[3] Documentation on pre-treatment device using ozonation, received from manufacturer in France

Method	Performance of method towards OPnEO/NPnEO and degradation products (literature data)
	the OP decomposition rate. Nitrate in the reaction solution lead to an increase of OP decomposition rate [8]. VUV (combined 253.7 nm and 184.9 nm) radiation was 100% more efficient on 4-t-OP degradation than UV radiation (253.7 nm). Factors influencing 4-tert-octylphenol degradation efficiency included solution pH, initial concentration and natural water constituents [9].
Electrolysis / anodic oxidation	Electrochemical oxidation may eliminate NPnEOs. However, no data on efficiency are given [10].
Activated carbon	50-90% efficiency towards OP [11][4] 25-99% efficiency towards NP [11][2] Furthermore, the sorption of NP to dissolved humic acids interferes with the removal of NP by activated carbon [12]. Approximately 3g Norit SAE Super activated carbon was required to adsorb 1g of OPnEO / NPnEO (activated carbon added in solution). 15 min incubation was sufficient for complete adsorption. There was no difference between 4 °C and room temperature. Buffer Salts: no difference between without, KPO4 and MES (2-(N-Morpholino)ethanesulfonic acid). Different activated carbon qualities showed different adsorption behaviour. The adsorption properties in "complex waste water" (e.g. presence of enzymes) were not investigated.[5]
ion exchange resin	NPnEO / OPnEO are not ions, hence adsorption is not expected

In summary, for many of the reviewed publications, it was not clear whether the described degradation process for the substances was complete or whether degradation products such as NP or OP were generated. In some instances, solutions after treatment (UV & ozone) became more toxic than before treatment (generation of toxic degradation products). Even production of OP was observed from solutions presumably containing OPnEO (ozonation; manufacturers' data). Furthermore, the efficiency of the methods regarding removal of the parent compounds OPnEO / NPnEO and the degradation products can vary substantially. Additionally, degradation efficiency seemed to depend on the composition of the solutions, e.g. the presence of organic matter (e.g., humic acids, but possibly also other organic matter present in IVD waste such as enzymes) caused a decrease in the OP decomposition rate and the presence of nitrate lead to an increase of OP decomposition rate (with UV radiation), although the presence of phosphate buffer or 2-(N-Morpholino)ethanesulfonic acid did not cause a difference in OPnEO/NPnEO adsorption by activated carbon.

[4] Untersuchungen zur Eliminierung gefährlicher Stoffe, Landesamt für Umwelt, Landwirtschaft und Geologie, Freistaat Sachsen, https://www.umwelt.sachsen.de/umwelt/wasser/download/120830_Schlussbericht_lfulg_spurenstoffe__endfassung.pdf

[5] Roche internal information

Composition of waste from IVD is complex and variable rendering any prediction of efficacy of treatment methods difficult. Substances known to be present in the waste solutions in addition to OPnEO / NPnEO are, for example, inorganic substances such as ammonium salt and sodium chloride, alcohols such as n-propanol and methanol, solvents such as acetonitrile and other simple organic molecules, as well as complex organics such as enzymes and material from the biological samples measured. All of these compounds could influence the efficiency of the methods / pre-treatment devices on OPnEO / NPnEO degradation. Also, presence of high COD concentrations in IVD liquid waste may decrease efficacy as other substances may be oxidized or adsorbed first. The composition of waste solutions varies greatly depending on the device and the analytical program used [1]. In addition, conditions in laboratory experiments as applied in published literature (e.g. treatment time, treatment intensity, composition of solutions) are seldom comparable with those in commercially available treatment devices (Table 1) and are more focused on conditions in STP effluents.

It has to be noted that some of the presented methods (in particular activated carbon) are also used for the treatment of STP effluents (see chapter 9.3.1.2.1 of this CSR (Use 3)), specifically in the STP in Mannheim, and a defined efficiency towards NP / OP removal is used for calculation of PEC values. Efficiency data, in particular of activated carbon treatment towards NP / OP removal from STP effluents are well-documented. However, no data on OPnEO / NPnEO removal by activated carbon in STPs were available. Hence, the efficiency of activated carbon treatment in the STPs towards OPnEO / NPnEO and all degradation products except for OP / NP was set to zero. Similarly, for the treatment devices no specific data on OPnEO or NPnEO removal are available.

In summary, the presented methods (Table 1) will likely be able to degrade some of the OPnEO / NPnEO present in the liquid waste (especially regarding the fact that most treatment devices employ more than one method alone, for example a combination of electrolysis with subsequent UV), even though complete degradation is unlikely and highly depends on the composition of the liquid waste and the method used. In addition, under certain conditions OP / NP or other degradation products may be generated during treatment (as indicated for example for one treatment device).

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Appendix 3

To CSR Use 3

Specific laboratory information for the UK, CC/DM and HIV

Specific laboratory information for UK, CC/DM and HIV

Laboratory No.	Type of instrument	separation of concentrated and diluted waste	amount of liquid waste / year	number of operating days / year	collection of liquid waste	treatment or pre-treatment of liquid waste	waste treatment costs for collected liquid waste fractions per year	waste treatment costs relative to annual revenue
UK-1	6x Cobas 8000 c702; 1x Cobas c513 analyser; 2x Cobas u700; 6x Cobas 8000 e801	no	appr. 131'400 L / year	360	no	no	data not available	data not available
UK-2	2x Cobas 8000 c702; 2x Cobas 8000 ISE module (double); 3x Cobas 8000 e602	no	appr. 61'000 L / year	360	no	no	data not available	data not available

Appendix 4

To CSR Use 3

Specific laboratory information for the UK, RTD

Specific laboratory information for UK - RTD

Laboratory No.	Type of instrument	amount of liquid waste / year	number of operating days / year	collection of liquid waste	treatment or pre-treatment of liquid waste	waste treatment costs for collected liquid waste fractions per year	waste treatment costs relative to annual revenue
UK-1	4x Benchmark Ultra; 2x Benchmark Special Stains	appr. 8'000 L/year	255	No	No treatment -release to sewer system, LCS (oil) separately	data not available	data not available
UK-2	5x Benchmark Ultra; 3x Benchmark XT; 1x Benchmark Discovery	appr. 12'000 L/year	255	No	No treatment -release to sewer system, LCS (oil) separately	data not available	data not available