CHEMICAL SAFETY REPORT

Legal name of applicant(s):	Roche Diagnostics International Ltd, Rotkreuz, Switzerland
Submitted by:	Roche Diagnostics International Ltd
Substances:	4-(1,1,3,3-Tetramethylbutyl)phenol, ethoxylated (covering well-defined substances and UVCB substances, polymers and homologues); (Octylphenolethoxylates, OPnEO).
Use titles:	Use of Octylphenolethoxylates in the Production of Sensors for Blood Gas and Electrolytes Analysis
Use number:	1

DECLARATION AND JUSTIFICATION OF CONFIDENTIALITY

We, Roche Diagnostics International Ltd, request that the information blacked out in this version of the Chemical Safety report is not disclosed to the public or any person requesting access to an official document. We hereby declare that, to the best of our knowledge, the blacked out fields comprise business or manufacturing secrets of our company ("Geschäfts- oder Fabrikations-geheimnisse" according to section 7, para. 1, lit. g of the Federal Act on Freedom of Information in the Administration). Disclosure could potentially enable competitors to adapt their own business or manufacturing practices based on data normally not available to them.

Signature: Alexander Martius Date, Place: Rotkreuz, 27-Jul-2022

Alexander Martius, LL.M., Head of Legal - Point of Care Customer Area

Signature: Dr. Jan Backmann Date, Place Basel, 27-Jul-2022

Dr. Jan Backmann MSc PhD, Head of Chemical Legislation

SUMMARY OF RISK MANAGEMENT MEASURES

The risk management measures applicable to the use of Octylphenolethoxylates in the production of sensors for blood gas and electrolytes analysis are stipulated in Section 2.4 of this 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 2.3.1 of the CSR.

DECLARATION THAT RISK MANAGEMENT MEASURES ARE IMPLEMENTED

The applicant declares that the risk management measures referred to in this CSR and described in Section 2 of the CSR are implemented by the submission date (July 2022)

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 sensors.

Table 1 Succinct summary of representative risk management measures and operational conditions: Exposure Scenario: IW1 – OPnEO – Use in sensor production

ECS and WCS	Task (ERC/spERC or PROC)	Annual amount per site (kg/a)	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: IW1 – OPnEO	PROC3 PROC8b PROC9	maximum expected [redacted]: 0.119	n.a. (environmentally hazardous substance)	n.a. (environmentally hazardous substance)	n.a. (environmentally hazardous substance)	n.a. (environmentally hazardous substance)	No release to wastewater No release to air expected due to low volatility Solid and liquid waste is collected and disposed of as hazardous waste	Water: 0% Air: 0% Soil: 0% Waste: 98.5%	2.3

Abbreviations: ECS=Environmental Contributing Scenario, WCS=Worker Contributing Scenario, IW=Industrial Worker, ERC=Environmental Release Category (or spERC (specific Environmental Release Category) if available), PROC= Process category, RMM=Risk Management Measure, LEV=Local Exhaust Ventilation, OSH=Occupational Safety and Health, PPE=Personal Protective Equipment

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GLOSSARY

Term	Explanation
AA-EQS	Annual average environmental quality standard
ACS	American Chemical Society
AfA	Application for Authorisation
AoA	Analysis of Alternatives
BGE	Blood gas and electrolyte BGE is part of the Point of Care Roche business unit and the affected products in this portfolio are the b 123 and the b 221 systems. BGE analysis is used in critical care settings such as Intensive care units (ICU), Emergency department (ED) and Neonatology. The measured parameters comprise pO_2, pCO_2, pH, Haematocrit, Na^+, K^+, Cl^-, Ca^{2+}, Glucose, Lactate, Urea/BUN. These critical parameters indicate for example whether oxygen is adequately delivered to tissues or help detecting jaundice in new-borns.
b 123 system	cobas® b 123 POC system
b 221 system	cobas® b 221 system
BUN	Blood Urea Nitrogen
CEC	Corporate Executive Committee
ChemO	Swiss Ordinance SR 813.11 on Protection against Dangerous Substances and Preparations (Chemicals Ordinance, ChemO) of 5 June 2015 (Status as of 5 May 2022).
CHF	Swiss Franc
CMC	Critical micelle concentration
cobas®	Trade name of Roche diagnostic system
Covid-19	Coronavirus disease of 2019
CSR	Chemical Safety Report
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
ECHA	European Chemicals Agency
ECS	Environmental Contributing Scenario
ED	Emergency Departments

Term	Explanation
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
EQS	Environment Quality Standard from the EU Water Frame Directive 2013/39/EU
ERC	Environmental Release Category
EU	European Union
FOEN	Federal Office for the Environment in Switzerland
FOPH	Federal Office of Public Health
GLU	Glucose
Hb	Haemoglobin
HDPE	High-density polyethylene
HLB	Hydrophilic-lipophilic balance
ICU	Intensive Care Units
ISE	Ion Selective Electrode
IVD	*In vitro* diagnostic medical devices. IVD products are regulated and defined by the Medical Devices Ordinance (MedDo) SR 812.213 of 1st of July of 2020 (Status as of 26 of May of 2021) as medical devices which are used as a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment or system in accordance with their specified purpose for the *in vitro* examination of specimens derived from the human body, including blood and tissue donations, and which are used solely or principally for the purpose of providing information: a. on physiological or pathological states; b. on congenital abnormalities; c. to determine safety and compatibility with potential recipients; d. to monitor therapeutic measures.
IVDR	EU Regulation concerning IVD medical devices Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on *in vitro* diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU (Status as of 28 January 2022
IW	Industrial Worker
LAC	Lactose

Term	Explanation
LEV	Local Exhaust Ventilation
MIO	Million
MSS	Metabolite Specific Sensor
NPT	Near Patient Testing
OCs	Operational Conditions
OP	Degradation product of OPnEO: 4-(1,1,3,3-tetramethylbutyl)phenol (4-tert-OP)
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]
ORRChem	Ordinance of the Swiss Federal Council on the Reduction of Risks relating to the Use of Certain Particularly Dangerous Substances, Preparations and Articles (Chemical Risk Reduction Ordinance, ORRChem) n° 814.81 of 18 May 2005.
OSH	Occupational Safety and Health
PEC	Predicted Environmental Concentration
PNEC	Predicted No Effect Concentration
PoC	Point of Care
PPE	Personal Protective Equipment
PROC	Process Category
Q1, Q2, etc.	Quartal 1, Quartal 2, etc.
QC	Quality Control
RAC	Committee for Risk Assessment
RDG	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).
RDI	Roche Diagnostics International Ltd (Rotkreuz, Switzerland)
REACH	Regulation on Registration Evaluation, Authorization and Restriction of Chemicals European Regulation (EC) No 1907/2006
RMMs	Risk Management Measures
SEA	Socio-economic Analysis
SECO	State Secretariat for Economic Affairs

Term	Explanation
spERC	Specific Environmental Release Category
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 REACH In fact, listing of a substance as an SVHC by the European Chemicals Agency (ECHA) is the first step in the procedure for limiting the use of a chemical (either with an authorization or a restriction)
sensor cartridge	Sensor Cartridges of the cobas® b 123
sensor cassette	Metabolite Specific Sensor (MSS) cassettes of the cobas® b 221 system: GLU/LAC/UREA (BUN) Cassette, GLU/LAC Cassette, GLU Cassette
UN SDGS	United Nations Sustainable Development Goals
UVCB	Substance of Unknown or Variable composition, Complex reaction products or Biological materials
WCS	Worker Contributing Scenario

Hazard Assessment

A report has been prepared to derive the Predicted No Effect Concentration (PNEC) or dose-response relationship for endocrine disrupting properties of OPnEO. It is documented in the supporting document SD1_Hazard_assessment_OPnEO. In this report, an indicative PNEC of 0.034 µg/L for freshwater is determined[1]. The environmental quality standard (AA-EQS) as defined by the European directive regarding priority substances in the field of water policy [2] is 0.1 µg/L.

[1] 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.

1 SUMMARY

The CSR was developed to support this application for temporary exemption pursuant to Annex 1.17 number 2 paragraph 4 ORRChem of Roche Diagnostics International (RDI) to continue the use of Octylphenolethoxylates (OPnEO) after the end of the transitional period until complete substitution. OPnEO is listed as entry 42 in Annex 1.17, paragraph 5 of the Swiss ORRChem. The end of the transitional period referred to is defined in Annex 1.17 as the 2 May 2024.

RDI is applying for a temporary exemption to continue the use of 119 g/year of OPnEO after the end of the transitional period until complete substitution. This CSR evaluates the following use:

Use 1: Use of Octylphenolethoxylates in the Production of Sensors for Blood Gas and Electrolytes Analysis

In this CSR, the applicant describes the use, the risk minimisation measures, the emissions and the mass balance of OPnEO in the manufacturing process of sensors for blood gas and electrolytes analysis (BGE). Data has been collected at the manufacturing site of RDI in Rotkreuz. This is the only manufacturing site for this kind of sensors in Switzerland for Roche. Initial data on the use of OPnEO was collected from manufacturing in 2020. Estimated figures for subsequent years are also taken into account.

A massflow analysis based on production data from 2020 and forecasted data [redacted] – where maximum OPnEO usage is expected – was performed. Activities and technical processes are described and assessed. With this combined analysis it can be shown that 98.5% of the OPnEO used in the production of the sensors is collected and incinerated. The 1.5% of OPnEO remains in the sensors and no emissions to the environment occur. Furthermore, end users of the sensors are advised to dispose of the used sensors as biohazardous waste. This waste must be processed according to local legislation. This results in no emissions to the environment at the end of the sensors' service life.

OPnEO was included into Annex 1.17 ORRChem because of the endocrine disrupting properties of the degradation products for the environment. Therefore, hazards to human health do not have to be considered in this assessment. As supplementary information, it is shown that exposure of OPnEO to workers (in the production as well as in the laboratories of the end users) and to consumers is either minimized by personal protective equipment (workers) or is zero since no direct contact is possible (end users).

2 Exposure Assessment

2.1 Introduction

The CSR was developed to support the application for temporary exemption pursuant to Annex 1.17 number 2 paragraph 4 ORRChem [1] of Roche Diagnostics International (RDI) to continue the use of Octylphenolethoxylates (OPnEO) after the end of the transitional period until complete substitution. OPnEO is listed as entry 42 in Annex 1.17 number 5 of the ORRChem. The end of the transitional period referred to is given in Annex 1.17 as the 2nd of May 2024.

The Federal Office for the Environment (FOEN) summarises the provisions of Annex 1.17 as follows[2]:

"…In line with the provisions of Annex XIV to REACH, the placing on the market and use of OPE (…) is subject to general bans, which come into force in Switzerland on 2 May 2024. As in the EU, the substances listed in Annex 1.17 (ORRChem) are prohibited, though they may be declared exempt from the ban in certain circumstances: authorisations granted by the EU Commission are regarded in Switzerland as exemptions from the prohibition, provided the substances concerned are placed on the market and used in accordance with the terms of the EU authorisation. Furthermore, the provisions of Annex 1.17 ORRChem stipulate that the Chemicals Registration Authority, in consultation with the Federal Office for the Environment (FOEN), the Federal Office of Public Health (FOPH) and the State Secretariat for Economic Affairs (SECO), may grant additional temporary exemptions for placing prohibited substances on the market and using them in Switzerland if alternative substances or procedures are not yet available…".

For the application for a temporary exemption the information requirements and subsequent guidance documents are in accordance with Article 62, paragraph 4-6 of Regulation 1907/2006/EC (REACH)[3]. Therefore, reference is made where applicable to EU requirements and guidance documents.

In this CSR the applicant describes the use, the risk minimisation measures, the emissions and the mass balance of OPnEO in the manufacturing process of sensors for blood gas and electrolytes analysis (BGE). Data has been collected at the manufacturing site of RDI in Rotkreuz. This is the only manufacturing site for this kind of sensors in Switzerland for Roche. Initial data on the use of OPnEO was collected from manufacturing in 2020, estimated figures for subsequent years are also taken into account.

The applicant will demonstrate emission minimisation and risk minimisation in this CSR. A predicted environmental concentration (PEC) could be compared with the AA-EQS of 0.1 µg/L [2] for surface waters as an indication of risk of OPnEO or OP to the environment. However, as it is shown that emissions to the environment are zero, a calculation of a risk quotient (e.g., PEC for surface waters divided by the environmental quality standard value (EQS)) is not necessary.

In this CSR, the applicant provides reliable estimates of environmental exposure based on releases from the production site. OPnEO was included into Annex 1.17 ORRChem due to endocrine disrupting properties. Also, in the RAC note from December 2017[3], the European Chemicals Agency (ECHA) confirmed that the focus should be on minimisation of the release of OPnEO to the environment with a focus on critical degradation products (i.e. OP) and that risk to human health does not need to be assessed for the purpose of the exposure assessment. As supplementary information, it is shown that consumers are not exposed to OPnEO contained in the sensors, and exposure to workers is minimised by usage of personal protection equipment. In Sections 2.3.4,

[2] https://www.bafu.admin.ch/bafu/en/home/topics/chemicals/info-specialists/chemicals--regulations-and-procedures/octylphenol--nonylphenol-and-their-ethoxylates.html
[3] Annex 1.17, number 2 paragraph 4 of the ORRChem [1]

2.3.5, and 2.3.6 this is further substantiated.

The applicant applies for a temporary exemption for the following use:

Use 1: Use of Octylphenolethoxylates in the Production of Sensors for Blood Gas and Electrolytes Analysis

2.2 Overview of Uses and Exposure Scenarios

2.2.1 Overview of Exposure Scenarios and Mass Balances

2.2.1.1 Overview of Exposure Scenarios

Table 2 Overview of exposure scenarios and contributing scenarios

Identifiers*)	Market Sector	Titles of exposure scenarios and the related contributing scenarios	Tonnage (tonnes per year)
IW1	SU 20: Health services SU0: Other – IVD assays PC0: article used as sensor in IVD assays	Production of Sensor Cartridges for Blood Gass and Electrolytes Analysis PROC3 - Use in closed batch process (synthesis or formulation) PROC8b - Transfer of substance or preparation (charging / discharging) from / to vessels / large containers at dedicated facilities PROC9 - Transfer of substance or preparation into small containers (dedicated filling line, including weighing)	0.000119
***) 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-#.)**			

2.2.1.2 Mass Balance and Evolution of Used Amounts Over Time

For the purpose of this CSR, the maximum annual usage as expected [redacted] serves as the annual amount applied for in this application for temporary exemption. Data for [redacted] are used, as the maximum usage of OPnEO is expected in that year based on the forecast (see Figure 1). The following table shows the mass balances for the year of data acquisition (2020) and the forecasted maximum OPnEO usage [redacted].

Table 3 Mass balance of OPnEO for 2020 and [redacted]

	Absolute amount per year 2020	Absolute amount per year [redacted]	Relative amount
Total amount	80 g	119 g	100%
Amount going to solid and liquid waste	78.8 g	117.2 g	98.5%
Amount remaining in sensors	1.2 g	1.8 g	1.5%
Amount going to wastewater	0 g	0 g	0%

From the submission date of the dossier to the end of the transitional period of 2nd of May 2024 and to the end of the review period, the total used amount of OPnEO at RDI in Rotkreuz is expected to vary mainly due to:

- Change in quantities of OPnEO required for the production of sensors in line with the number of tests performed and the maximum in-use time of the specific sensors
- Planned substitutions of the systems using these sensors

In the following figure the forecasted data on OPnEO usage from 2020 onwards is shown. [redacted].

Figure 1 Evolution of the total annual use of OPnEO between 2020 and [redacted]

2.3 Introduction to the Assessment

In this section the use of OPnEO for the production of the sensors is described. All preparational and manufacturing steps are explained and potential releases to the environment are addressed.

The usage of the sensors in different systems produced by RDI is described in Section 3 of the Analysis of Alternatives (AoA) which is also part of this application.

2.3.1 Description of the Activities and Technical Processes to Produce the Sensors

STEP 1: Triton X-305 (a solution of 70% OPnEO in water) as received from the supplier is stored in the original polyethylene containers in a refrigerated cabinet. Triton X-305 is treated as an end-of-life material, which is long-term stored until complete usage or exceeding the expiry date. For all steps involving a room-to-room transport, a trolley and special box for transport of chemicals are used. The required amount of Triton X-305 [redacted] is being manually weighed from the original containers under a fume hood by using a [redacted] spatula. The [redacted] apparatus consists of two parts, a reactor and a pre-mixer (Figure 2) and for both compartments a separate solution containing Triton X-305 and other reagents is prepared.

Figure 2 Apparatus used for the [redacted] synthesis

For the reactor solution, Triton X-305 [redacted] is transferred to a [redacted] and mixed with other reagents, then stirred and heated to dissolve the reagents. This emulgator solution is filled into the reactor using a funnel, where it is stirred again. Similarly, for the preparation of the emulgator solution for the pre-mixer Triton X-305 [redacted] is transferred to a [redacted] and mixed with other reagents. A second solution for the pre-mixer contains the monomers for the subsequent polymerisation. Both solutions are mixed in the pre-mixer by circulating with a membrane pump. After mixing [redacted] of this monomer-emulsion are filled into a glass beaker and [redacted] is transferred to the reactor using a glass funnel. The rest of the glass beaker contents is transferred to the pre-mixer. [redacted] of polymerisation starters are added to the pre-mixer and the reactor prior to pumping the complete contents of the pre-mixer slowly into the reactor. Within the reactor a synthesis forming the [redacted] is occurring in a slight exothermic reaction. After adding [redacted], the [redacted] is filled into a glass beaker using the bottom valve of the reactor, and the [redacted] is filtered [redacted] and filled into a [redacted] bottle. Part of this solution is filled into a brown wide neck bottle [redacted] which is used for quality control. The [redacted] bottle is stored [redacted] in a special cabinet and is regularly opened ([redacted]) and mixed using a shaking apparatus [redacted]. Before usage of the [redacted] emulsion (see step 2) 10 ml aliquots are taken for laboratory testing (release approval for manufacturing).

[redacted]

The [redacted] apparatus is solely used to produce the [redacted] emulsion and all work is performed under a fume hood. Upon use of the apparatus several cleaning steps with Aceton/Ethanol and distilled water are applied. All surplus, liquid waste and cleaning residues are collected in a canister for special chemical waste (incinerated by disposal contractor). After the preparation of the [redacted] emulsion, all reusable glassware including the apparatus itself and the used glassware (beakers, funnels) are cleaned with Aceton/Ethanol, then three washing steps with distilled water are applied. Afterwards all pre-cleaned glassware is washed with a dishwasher. The dishwasher is connected to the wastewater system but due to the pre-cleaning of the glassware it is not expected that relevant amounts of OPnEO might be transferred to the wastewater. All solid waste including empty original containers and filters are collected and disposed as special chemical waste. During the operations, spilling is not expected to occur. In case of small spilling, drops of the solution may be spilled which would be absorbed with binding material (disposal as special chemical waste).

STEP 2: The [redacted] emulsion which was synthesized during step 1 is used to produce [redacted] emulsion needed for the sensors of cobas® b 123 and cobas® b 221 systems. For this, small

amounts of the ripened [redacted] emulsion are pipetted into a [redacted] vial and mixed [redacted]. The working station (precision balance and waste container for pipette tips) is shown in Figure 3

Figure 3 Working station to mix the [redacted] emulsion includes a waste container

After this procedure the vial is closed [redacted] and the [redacted] emulsion is transferred to the working station for the next step (transfer onto sensors) using a trolley and box for transport of chemicals. All liquid and solid waste (e.g. pipette tips) are disposed of as special waste and all glassware is pre-cleaned and washed as described in step 1.

[redacted]

STEP 3: During this step the [redacted] emulsion is transferred onto the sensors using an automated processing system (Figure 4). For this, the [redacted] emulsion is filled into a special glass syringe. In case of spilling during the filling of the glass syringe it will be wiped using tissues for cleaning. The glass syringe is installed in the automated processing system where the emulsion is dispensed onto the sensors. After dispensation of the emulsion [redacted] a solid membrane is formed on the sensors. After the dispensation step the glass syringe is cleaned and dried with isopropanol. The needle and other solid waste (e.g. wiping tissues, plastic material) is disposed of as special waste. Liquid waste from cleaning is collected in a separate chemical waste container and disposed of as special waste. After use of the processing system, it is manually cleaned by wiping with tissues in case of small spillings.

Figure 4 Processing line to transfer the [redacted] solution onto the sensors

2.3.1.1 Quality Control

Once the final sensors are produced, sample sensors are taken to be checked for quality using a cobas® b 221 system (measurement of 18 parameters for blood gas and electrolyte analysis) and cobas® b 123 POC system (17 parameters). The quality control requires the use of blood samples. The waste fluids are collected in the waste container integrated in the systems. Thus, all liquid waste which was in contact with sample is biohazardous waste (incinerated by a disposal contractor). Further, all solid waste including the sensors and fluid boxes are disposed of as biohazardous waste. Liquid and solid waste occurring during quality control which was not in contact with sample is incinerated as special waste.

2.3.1.2 Disposal by End Users

All end users (e.g., hospitals, laboratories) are required to ensure disposal of chemical and biohazardous waste according to local regulations.

2.3.1.3 Summary of Waste Handling During Sensor Production

During the production of sensors, all liquid and solid waste which was in contact with OPnEO are sent to the waste disposal station and are either incinerated as special or as biohazardous waste. No potential OPnEO release from liquid and solid waste can occur during production at the site. The only potential release is from the dishwashing of pre-cleaned glassware. The wastewater from the dishwashing machine is directly released to the internal wastewater channel of the building. The collection of the rinsing waters from the dishwater is not possible with the current setup of installation. However, release of OPnEO from dishwashing of pre-cleaned glassware is negligible since the pre-washing steps (see description during the process steps) are designed to remove residues from the glassware.

2.3.2 Usage of sensor cartridges in cobas® systems

The sensors are used in cartridges or cassettes for the cobas® b 123 POC systems and cobas® b 221 systems, respectively. Such use takes place during QC in the production at Rotkreuz as well as through professional users operating the systems in laboratories or hospitals. For the initial placement of the cartridges/cassettes in the system and replacement after the maximum in-use time of the sensors has been reached, the instructions for use of these systems advise the operator to wear personal protective equipment. The maximum in-use time depends on the specific sensor configuration and the number of tests performed (typically, it is in the range of 7 to 28 days). It is

also stated in the instructions that these sensor cartridges may contain trace amounts of hazardous liquids and inappropriate handling may lead to direct exposure of these liquids. However, during normal operation, the operator is not exposed to the sensor, or the fluids contained in the sensor but solely to the plastic material forming the cartridge or cassette (see Figure 5).

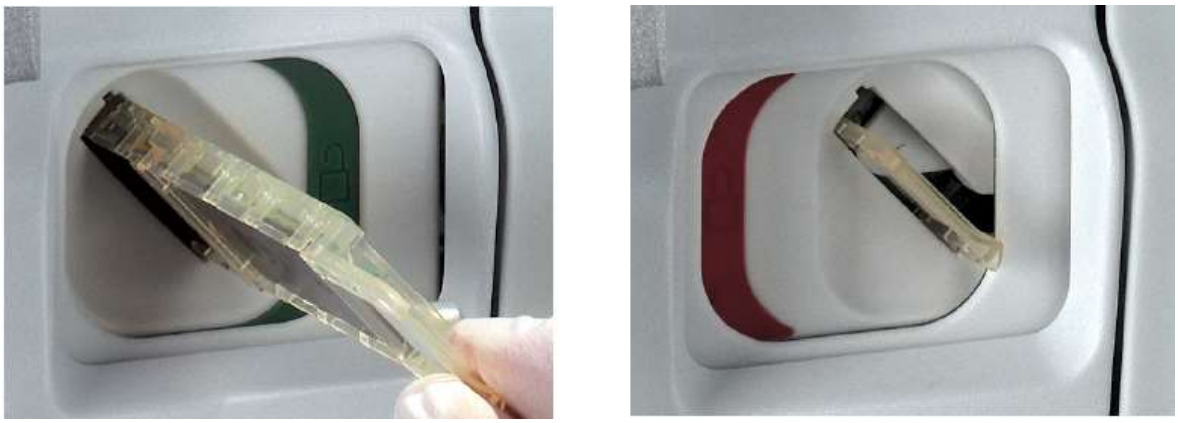

Figure 5 Placement of a sensor cartridge into the cobas® 123 system [4]

2.3.3 Environment

The release of OPnEO was estimated based on data collected on the manufacturing process at RDI considering RMMs which are implemented (see Section 2.3.1). For the sensor manufacturing, direct and indirect releases of OPnEO to the environment do not occur. Therefore, a risk characterisation is not needed.

2.3.4 Man via the environment

In the RAC note from December 2017[3], the European Chemicals Agency (ECHA) confirmed that the focus of the assessment should be on minimisation of the release of OPnEO to the environment also taking into account critical degradation products (i.e. OP) and that risk to human health does not need to be assessed for the purpose of the exposure assessment. Therefore, exposure of man via the environment was considered out of scope of the assessment.

Furthermore, since no emissions of OPnEO/OP to the environment occur during the manufacturing of the sensors at RDI and the final use in laboratories and hospitals the exposure to man via the environment is also zero.

2.3.5 Workers

Exposure of workers to OPnEO/OP used during production of the sensors for BGE or OPnEO/OP contained in the sensors does not have to be assessed since the properties that led to the inclusion of OPnEO into Annex 1.17 are entirely based on environmental hazards and not on hazards to human health.

In the following general risk management measures to prevent worker exposure to hazardous substances established at Roche and advised for the use of the sensors are described as supplementary information.

Roche has established standard operating procedures on safety classes and corresponding personal protective equipment as well as on material and waste management. Personnel is trained via classroom courses and/or e-learnings. The completion of these courses is tracked in a software to ensure everybody has passed the requested trainings. This ensures compliance with all internal and external obligations regarding safety of the employees and regarding the safe handling of all

materials and waste.

Also, operators of the systems equipped with OPnEO-containing sensor cartridges are advised in the instructions of use to these systems to always wear appropriate personal protective equipment, such as lab gloves, lab coat, eye protection, and face shield if there is a chance of splashing or splattering [4]. Even though, in normal operation of the systems, exposure to OPnEO is not possible, wearing of protective equipment prevents exposure of the operators to OPnEO in situations where breakage of the sensor cartridges may occur (e.g., during the exchange of the sensor cartridges, see Figure 5).

2.3.6 Consumers

Exposure of consumers to OPnEO does not have to be assessed since the properties that led to the inclusion of OPnEO into Annex 1.17 are entirely based on environmental hazards and not on hazards to human health.

Nonetheless, it should be noted that consumers are not exposed to the OPnEO contained in the sensors. Blood samples from patients are processed in the system containing the sensors and solid and liquid waste from this processing is disposed of either as hazardous or as biohazardous waste according to local legislation. There is no direct contact of the consumer, i.e., patients, with the instruments or the sensors or with the OPnEO contained in the sensors. Since there are no emissions to the environment, there is also no exposure of consumers to OPnEO from sensors via the environment.

2.4 Exposure Assessment for OPnEO

2.4.1 Exposure Scenario 1: IW1

2.4.1.1 Environmental Contributing Scenario

2.4.1.1.1 Conditions of Use

The following table summarises the conditions of use which are implemented at the RDI manufacturing site at Rotkreuz. Details on the technical and organisational measures to minimise releases to the environment are provided in Section 2.3.1

Amount used, frequency and duration of use (or from service life)
Total tonnage (g/a): 119
Percentage of total tonnage used at regional scale: 100 %
Fraction of regional tonnage used at local scale: 1
Annual site tonnage (g/a): 119
Maximal number of emission days (d/a): 0 (no emissions to the environment)
Maximum daily site tonnage (g/d): [redacted]
Type of release: no release to the environment
Technical and organisational conditions and measures
Surplus/solid waste is collected and incinerated in an incinerator
Handling only by trained personnel
All steps take place in a highly controlled environment
Conditions and measures related to external treatment of waste (including article waste)
The surplus/solid waste/sensors for quality control are collected and incinerated in an industrial waste incinerator
Conditions and measures related to external recovery of waste (including article waste)
No waste recovery (incineration in an industrial waste incinerator)
Other conditions affecting environmental exposure
see Section 2.3.1
Additional good practice advice.
Specific SOP documents have been created for all manufacturing steps

2.4.1.1.2 RMM Implemented

Risk management measures are implemented at the RDI site in Rotkreuz to prevent emissions of OPnEO to the environment during the production of sensors. These RMMs include:

- collection of all solid waste and subsequent incineration either as hazardous or biohazardous waste
- collection of liquid waste and subsequent incineration either as hazardous or biohazardous waste
- pre-cleaning of glassware, designed to remove traces of OPnEO from glassware in contact with OPnEO. Only pre-cleaned glassware (that was in contact with OPnEO) is finally cleaned using dish washers connected to the wastewater system of the site

2.4.1.1.3 Releases

The following table summarises the estimated emissions of OPnEO to the environment.

Table 4 Local releases to the environment

Compartment	Release factor estimation method	Explanation / Justification
Water	based on specific data from the production site	Release factor: 0 % Local release rate: 0 g/d Explanation / Justification: release factor determined based on the data collected considering RMMs (i.e. collection and incineration of waste and no emissions to wastewater)
Air	based on substance-specific data and data from the production site	Release factor: 0 % Local release rate: 0 g/d Explanation / Justification: OPnEO is not volatile (Vp = 1.8×10^{-14} mmHg, [1])
Soil	based on specific data from the production site	Release factor: 0 % Local release rate: 0 g/d Explanation / Justification: There is no direct release to soil

Releases to Waste

Maximum releases to waste from production of the sensors (estimated [redacted]) are 117.2 g OPnEO. All waste from the manufacturing site is incinerated, hence no environmental emissions are expected from waste.

The sensor cartridges and cassettes are labelled as biohazardous material and should be disposed of according to local and/or laboratory regulations when replaced with new cartridges [4]. In Switzerland hazardous medical waste may only be submitted to special collection points or licensed waste disposal operations. This guarantees that the waste is disposed of under controlled conditions in a suitable facility [5].

3 Conclusion

The maximum amount used at RDI in Rotkreuz is forecasted to be 119 g [redacted].

Based on the mass balance and the description of the activities and technical processes it could be shown that emissions of OPnEO to the environment do not occur during the production of the sensors: 98.5% of the OPnEO is collected and incinerated as hazardous waste and 1.5% is remaining in the sensors. All solid and liquid waste from the production is collected as hazardous waste and incinerated. All glassware used in the production that was in contact with OPnEO is pre-cleaned in a procedure to ensure that residues of OPnEO do not enter the sewer system when final cleaning in a dishwasher takes place. After use, the sensor cartridges and cassettes must be disposed of as biohazardous waste. By this, emissions of OPnEO to the environment do not occur at the end-of-life of the sensor cartridges and cassettes.

4 REFERENCES

[1] The Swiss Federal Council, Ordinance on the Reduction of Risks relating to the Use of Certain Particularly Dangerous Substances, Preparations and Articles (Chemical Risk Reduction Ordinance, ORRChem), May 2005, status as of 1 May 2022

[2] European Commission, DIRECTIVE 2013/39/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 12 August 2013 amending Directives 2000/60/EC and 2008/105/EC as regards priority substances in the field of water policy (EU Water Framework Directive)

[3] ECHA (2018) Committee for Risk Assessment, Risk-related considerations in applications for authorisation for endocrine disrupting substances for the environment, specifically OPnEO and NPnEO (Agreed at RAC-43)

[4] Roche Diagnostics, cobas® b 123 POC System – Instructions for Use, Version 13.0, cobas® b 221 System – Instructions for Use, Version 18.0

[5] Federal Office for the Environment (FOEN), Entsorgung von medizinischen Abfällen, Bern 2021