Committee for Risk Assessment (RAC)

Committee for Socio-economic Analysis (SEAC)

Opinion

on an Application for Authorisation for

4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated

(4-tert-OPnEO or 4-OPE)

for

Use 1:

Industrial use of 4-tert-OPnEO for its non-ionic detergent properties in the formulation of reagents for molecular *in vitro* preparative and testing applications

Submitting applicant: bioMérieux SA

ECHA/RAC/SEAC: AFA-O-0000006885-60-01/F

Consolidated version

Date: 02/12/2020

Consolidated version of the Opinion of the Committee for Risk Assessment and Opinion of the Committee for Socio-economic Analysis on an Application for Authorisation

Having regard to Regulation (EC) No 1907/2006 of the European Parliament and of the Council 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (the REACH Regulation), and in particular Chapter 2 of Title VII thereof, the Committee for Risk Assessment (RAC) and the Committee for Socio-economic Analysis (SEAC) have adopted their opinions in accordance with Article 64(4)(a) and (b) respectively of the REACH Regulation with regard to the following application for authorisation:

Applicant	**bioMérieux SA** (position in supply chain: downstream)
Substance ID EC No CAS No	4-(1,1,3,3-Tetramethylbutyl)phenol, ethoxylated (in what follows referred to as 4-tert-OPnEO) - -
Intrinsic properties referred to in Annex XIV	☐Carcinogenic (Article 57(a)) ☐Mutagenic (Article 57(b)) ☐Toxic to reproduction (Article 57(c)) ☐Persistent, bioaccumulative and toxic (Article 57(d)) ☐Very persistent and very bioaccumulative (Article 57(e)) ☒Other properties in accordance with Article 57(f): Endocrine disrupting properties – environment
Use title	Use 1: Industrial use of 4-tert-OPnEO for its non-ionic detergent properties in the formulation of reagents for molecular in vitro preparative and testing applications
	Other connected uses: Use 2: Industrial use of 4-tert-OPnEO for its non-ionic detergent properties to control the level of non-specific reactions in the formulation of in vitro reagents for clinical and industrial in vitro testing immunoassays Use 3: Industrial use of 4-tert-OPnEO for its detergent properties, used for the extraction of biological material which is further formulated and intended for clinical and industrial in vitro testing applications
	Same uses applied for: Not applicable
Use performed by	☒Applicant ☐Downstream User(s) of the applicant

Use ID (ECHA website)	0143-01
Reference number	11-2120809115-64-0001
RAC Rapporteur RAC Co-rapporteur	VAN DER HAAR Rudolf LEINONEN Riitta
SEAC Rapporteur	LEAHY Eimear and (consecutively) SHAKHRAMANYAN Nikolinka
ECHA Secretariat	REGIL Pablo GMEINDER Michael PENNESE Daniele LUDBORŽS Arnis

PROCESS INFORMATION FOR ADOPTION OF THE OPINIONS

Date of submission of the application	20/02/2019
Date of payment, in accordance with Article 8 of Fee Regulation (EC) No 340/2008	20/05/2019
Application has been submitted by the Latest Application Date for the substance and applicant can benefit from the transitional arrangements described in Article 58(1)(c)(ii)	☒ Yes ☐ No
Consultation on use, in accordance with Article 64(2): https://echa.europa.eu/applications-for-authorisation-previous-consultations	22/05/2019 - 17/07/2019
Comments received	☒ Yes ☐ No Link: https://echa.europa.eu/applications-for-authorisation-previous-consultations/-/substance-rev/23326/del/200/col/synonymDynamicField_302/type/asc/pre/2/view
Request for additional information in accordance with Article 64(3)	17/05/2019 (RAC) 22/05/2019 (SEAC) 04/07/2019 (SEAC) 31/07/2019 (SEAC) Link: https://echa.europa.eu/applications-for-authorisation-previous-consultations/-/substance-rev/23326/del/200/col/synonymDynamicField_302/type/asc/pre/2/view
Trialogue meeting	Not held – Not needed considering responses of applicant to comments received during consultation and responses of applicant to RAC and SEAC requests for additional information
Extension of the time limit set in Article 64(1) for the sending of the draft opinions to the applicant	☐ Yes ☒ No
The application included all the necessary information specified in Article 62 that is relevant to the Committee's remit	☒ Yes ☐ No
Date of agreement of the draft opinion in	RAC: 05/12/2019, agreed by consensus.

accordance with Article 64(4)(a) and (b)	SEAC: 20/09/2019, agreed by consensus.
Date of sending of the draft opinion to applicant	07/02/2020
Date of decision of the applicant to comment on the draft opinion, in accordance with Article 64(5)	17/02/2020 Decision of the applicant to comment in order to provide a substitution plan 30/05/2020 Decision of the applicant to comment to update information based on COVID-19 related activities
Date of receipt of comments in accordance with Article 64(5)	14/04/2020 Substitution plan 30/09/2020 COVID-19 related update
Date of adoption of the opinion in accordance with Article 64(5)	RAC: 02/12/2020, adopted by consensus.
	SEAC: 30/11/2020, adopted by consensus.
Minority positions	RAC: ☒N/A
	SEAC: ☒N/A

THE OPINION OF RAC

RAC has formulated its opinion on:

- the risks arising from the use applied for,
- the appropriateness and effectiveness of the risk management measures described, as well as
- other available information.

In this application, the applicant did not derive PNEC(s). Therefore, RAC concluded, in accordance with Annex I of the REACH Regulation, that for the purposes of the assessment of this application it was not possible to determine PNEC(s) for the endocrine disrupting properties for the environment of the substance.

SEAC concluded that currently there are no technically and economically feasible alternatives available for the applicant with the same function and similar level of performance. Therefore, RAC did not evaluate the potential risk of alternatives.

RAC concluded that the operational conditions and risk management measures described in the application are appropriate and effective in limiting the risk, provided that they are adhered to.

The recommendations for the review report are expected to allow RAC to evaluate the review report efficiently.

The use applied for may result in emissions of 2.08 kg/year of the substance to the environment.

THE OPINION OF SEAC

SEAC has formulated its opinion on:

- the socio-economic factors, and
- the suitability and availability of alternatives associated with the use of the substance as documented in the application, taking into account the information submitted by interested third parties, as well as
- other available information.

SEAC took note of RAC's conclusion that it is not possible to determine a PNEC for the endocrine disrupting properties for the environment of the substance in accordance with Annex I of the REACH Regulation.

The following alternatives have been assessed (see section 4 of the justifications to this opinion): Six non-ionic detergents, names claimed confidential by the applicant.

SEAC concluded on the analysis of alternatives that:

- By the Sunset Date there are no alternatives available with the same function and similar level of performance that are safer and technically and/or economically feasible for the applicant.
- The substitution plan is credible and consistent with the analysis of alternatives and the socio-economic analysis.

SEAC concluded on the socio-economic analysis that:

- The expected socio-economic benefits of continued use are at least €10-75 million per year and additional benefits to society have been assessed qualitatively but have not been monetised. These additional benefits comprise avoided health related impacts

resulting from unavailability of NucliSens® extraction products and NucliSens® easyQ® HIV-1 products.

- Risks to the environment of shortlisted alternatives have not been quantified. There may therefore be a risk arising due to the use of an alternative should the authorisation not be granted.

SEAC has no substantial reservations on the quantitative and qualitative elements of the applicant's assessment of the benefits and the risks to the environment associated with the continued use of the substance.

SEAC considered that if an authorisation was refused, the use of the substance could:

- cease altogether
- be substituted by market actors operating inside the EU
- be taken up by market actors operating outside the EU

SEAC considered that, if an authorisation was refused, it was likely that in the European Union:[1]

- 8.6 jobs would be lost

PROPOSED CONDITIONS AND MONITORING ARRANGEMENTS, AND RECOMMENDATIONS

No additional conditions for the authorisation or monitoring arrangements for the authorisation are proposed.

Recommendations for the review report are made. These are listed in section 9 of the justification to this opinion.

REVIEW PERIOD

Taking into account the information provided in the application for authorisation submitted by the applicant and the comments received on the broad information on use, a **12-year** review period is recommended for this use.

[1] Wherever reference is made to the European Union, this shall apply also to EEA countries.

SUMMARY OF THE USE APPLIED FOR

Role of the applicant in the supply chain	Upstream ☐ [group of] manufacturer[s] ☐ [group of] importer[s] ☐ [group of] only representative[s] ☐ [group of] formulator[s] Downstream ☒ downstream user
Number and location of sites covered	1 site in Grenoble, France
Annual tonnage of Annex XIV substance used per site (or total for all sites)	ES-1: 6,500 kg/year ES-2: 0.0092 kg/year
Function(s) of the Annex XIV substance	In the context of Use 1 the main functionalities of 4-tert-OPnEO are detergency in mild conditions, ability to disrupt cellular membranes and then, to solubilize and to stabilize proteins or enzymes and concomitant pathogen inactivation properties according to the kind of cellular materials to be diagnosed.
Type of products (e.g. articles or mixtures) made with Annex XIV substance and their market sectors	**NucliSens® extraction range:** Four different buffer solutions (extraction and lysis buffers) involved in the preparation of nucleic acids by extraction from biological specimens (e.g. human fluids, veterinary or food samples) further used in different in vitro diagnostic (IVD) and non-IVD applications. These buffer solutions are used on EMAG™, easyMAG®, miniMAG™ and eGENE-UP® extraction platforms. EMAG™, easyMAG® and miniMAG™ are dedicated to clinical use, while eGENE-UP® is used in the industrial sector (food, pharmaceutical, veterinary, cosmetic). From the year 2020, buffer solutions are also used in the easyMAG® and EMAG™ systems for COVID-19 molecular testing and for commercial SARS-CoV-2 molecular assays. **NucliSens® easyQ®:** One enzymatic reagent used in the process of amplification of ribonucleic acid (RNA), in HIV diagnosis and follow-up.
Shortlisted alternatives discussed in the application	Alternative substances considered: Six non-ionic detergents shortlisted, names claimed confidential by the applicant Alternative technologies considered: None Others: None

Annex XIV substance present in concentrations above 0.1 % in the products (e.g. articles) made	☒ Yes ☐ No ☐ Unclear ☐ Not relevant
Releases to the environmental compartments	☐ Air ☒ Water ☐ Soil ☐ None
The applicant has used the PNEC recommended by RAC	☐ Yes ☐ No ☒ Not relevant
All endpoints listed in Annex XIV were addressed in the assessment	☒ Yes ☐ No
Adequate control demonstrated by applicant for the relevant endpoint(s)	☐ Yes ☐ No ☒ Not Applicable – non-threshold substance
Level of (combined, daily) exposure/release used by applicant for risk characterisation	<u>Release</u> Water: • 2.08 kg/year (ES-1) (monitoring) • 0.000183 kg/year (ES-2) (ERC2) Air: 0 g/year (emissions to air are considered negligible, because of the relatively low vapour pressure of the substance of < 0.01 hPa at 20 °C) Soil: 0 g/year (direct release to soil is considered negligible)
Risk characterisation	Environmental compartments: The applicant did not attempt to derive PNECs or RCRs and has treated 4-tert-OPnEO as a non-threshold substance. The CSR describes how the operational conditions (OCs) and risk management measures (RMMs) in the Exposure Scenarios (ES) prevent or minimise releases to the environment as far as technically and practically possible (with the view to minimising the likelihood of adverse effects).

Applicant is seeking authorisation for the period of time needed to finalise substitution ('*bridging application*')	☐ Yes ☒ No ☐ Unclear
Review period argued for by the applicant (length)	12 years
Most likely Non-Use scenario	Cessation of production of NucliSens® extraction products and NucliSens® easyQ® HIV-1 products
Applicant concludes that benefits of continued use outweigh the risks of continued use	☒ Yes ☐ No ☐ Not Applicable – threshold substance with adequate control
Applicant's benefits of continued use As recalculated by SEAC	Avoided profit loss: €10-225 million (over the requested review period)
Society's benefits of continued use As reported by the applicant	Avoided job loss: €0.3 million (over the requested review period) Avoided health related impacts resulting from unavailability of NucliSens® extraction products and NucliSens® easyQ® HIV-1 products
Job loss impacts if authorisation is not granted As reported by the applicant	8.6

SUMMARY OF RAC AND SEAC CONCLUSIONS[2]

1. Operational Conditions and Risk Management Measures

1.1. Conclusions of RAC

Are the OCs/RMMs in the Exposure Scenario appropriate and effective in limiting the risk?

☒Yes ☐No

Conclusion for environment

All devices, which had been in contact with 4-tert-OPnEO, are collected and disposed of as waste for incineration and the relevant wastewater is collected for incineration, therefore no relevant shortcomings to the operational conditions (OCs) and risk management measures (RMMs) have been identified.

Does RAC propose additional conditions related to the operational conditions and risk management measures for the authorisation?

☐Yes ☒No

Does RAC propose monitoring arrangements related to the operational conditions and risk management measures for the authorisation?

☐Yes ☒No

Does RAC make recommendations related to the operational conditions and risk management measures for the review report?

☒Yes ☐No

2. Exposure Assessment

Conclusions of RAC:

RAC considers, on balance, that the release estimates provided by the applicant are appropriate. RAC did not identify shortcomings in the methodology used by the applicant to estimate the release (that cannot be addressed by further measurements), that would invalidate this conclusion.

Does RAC propose additional conditions[3] related to exposure assessment for the authorisation?

☐Yes ☒No

[2] The numbering of the sections below corresponds to the numbers of the relevant sections in the Justifications.
[3] Conditions can be proposed where the RCR is > 1 and the risk is therefore not adequately controlled, or the OCs and RMMs are not appropriate and effective in limiting the risk and therefore the minimisation of emissions has not been not demonstrated.

Does RAC propose monitoring arrangements[4] related to exposure assessment for the authorisation?

☐Yes ☒No

Does RAC make recommendations related to exposure assessment for the review report?

☒Yes ☐No

3. Risk Characterisation

Conclusions of RAC:

The applicant has treated 4-tert-OPnEO as a non-threshold substance and did not attempt to derive PNECs or RCRs. This approach is in line with RAC's paper *"Risk-related considerations in applications for authorisation for endocrine disrupting substances for the environment, specifically OPnEO and NPnEO"*, adopted at RAC-43[5] and RAC's conclusion at its 50th meeting that it is currently not possible to determine a threshold for the ED properties of this substance.

RAC is of the view that the applicant have demonstrated that releases to environmental compartments have been prevented or minimised as far as is technically and practically possible (with the view to minimising the likelihood of adverse effects), considering the OCs & RMMs in the exposure scenario (ES), notably the use of 4-tert-OPnEO in mainly closed systems and the incineration of solid and liquid wastes.

The use applied for may result in emissions of 2.08 kg/year (monitoring data).

4. Analysis of alternatives and substitution plan[6]

What is the amount of substance that the applicant uses per year for the use applied for?

6,500 kg/year

Are there alternatives with the same function and similar level of performance that are technically and economically feasible to the applicant before the Sunset Date?

☐Yes ☒No

Has the applicant submitted a substitution plan?

☒Yes ☐No

[4] Monitoring arrangements can be recommended where RCR is < 1, OCs and RMMs are appropriate and effective, risk is adequately controlled, minimisation of emissions is demonstrated – but minor concerns were identified.

[5] https://echa.europa.eu/documents/10162/13637/npneo_and_opneo_for_agreement_final_en.pdf/026cbafc-6580-1726-27f3-476d05fbeef0

[6] The judgment of the ECJ Case T-837/16 Sweden v Commission stated that the applicant has to submit a substitution plan if alternatives are available in general. The Commission is currently preparing the criteria, derived from the judgment for establishing when an alternative is available in general. Once these are prepared this opinion format will be amended accordingly. The European Commission informed the REACH Committee in 9-10 July 2019 of its preliminary views on the criteria. In that note that Commission considered that the criteria defining a 'suitable alternative' would imply that it was i) *safer* and ii) *suitable*. Suitability would not mean it to be "*in abstracto*" or "*in laboratory or exceptional conditions*" but it should be "*technically and economically feasible in the EU*" and "*available, from the point of view of production capacities of the substance or feasibility of the technology, and legal and factual conditions for placing on the market*".

If yes, is the substitution plan credible and consistent with the analysis of alternatives and the socio-economic analysis?

☒Yes ☐No

Conclusions of SEAC

By the sunset date there are no alternatives available with the same function and similar level of performance that are safer and technically and/or economically feasible for the applicant. The substitution plan is credible and consistent with the analysis of alternatives and the socio-economic analysis.

Does SEAC propose any additional conditions or monitoring arrangements related to the assessment of alternatives for the authorisation?

☐Yes ☒No

Does SEAC make any recommendations to the applicant related to the content of the potential review report?

☐Yes ☒No

5. Benefits and risks of continued use

Has the applicant adequately assessed the benefits and the risks of continued use?

Conclusions of SEAC:

☒Yes ☐No

SEAC has no substantial reservations on the quantitative and qualitative elements of the applicant's assessment of the benefits and the risks to the environment associated with the continued use of the substance. This conclusion is made on the basis of:

- the application for authorisation,
- SEAC's assessment of the benefits of continued use,
- SEAC's assessment of the availability, technical and economic feasibility of alternatives,
- SEAC's assessment of the comments received in the consultation,
- any additional information provided by the applicant,
- RAC's assessment of the risks to the environment.

6. Proposed review period for the use

☐ 4 years

☐ 7 years

☒ 12 years

☐ Other – … years

7. Proposed additional conditions for the authorisation

RAC

Additional conditions:

For the environment ☐Yes ☒No

SEAC

Additional conditions: ☐Yes ☒No

8. Proposed monitoring arrangements for the authorisation

RAC

Monitoring arrangements:

For the environment ☐Yes ☒No

SEAC

Monitoring arrangements ☐Yes ☒No

9. Recommendations for the review report

RAC

For the environment ☒Yes ☐No

SEAC

AoA ☐Yes ☒No

SEA ☐Yes ☒No

10. Applicant comments on the draft opinion

Has the applicant commented the draft opinion?

☒Yes ☐No

Has action been taken resulting from the analysis of the applicant's comments?

☒Yes ☐No

JUSTIFICATIONS

0. Short description of use

0.1. Description of the process in which Annex XIV substance is used

bioMérieux applied for the industrial use of 4-tert-OPnEO for its non-ionic detergent properties in the formulation of reagents for molecular *in vitro* preparative and testing applications (Use 1).

The use is performed at one site with two exposure scenarios:

- ES-1: Production of reagents for Total Nucleic Acid Extraction at Grenoble, France, using Triton® X-100 for molecular biology.
- ES-2: Production of reagents for clinical IVD testing applications at Grenoble, France, using Triton® X-100 which is included in commercial intermediate raw material, enzymes, by the manufacturer to stabilize the mixture. Additional Triton® X-100 is added during the formulation of a mix to maintain an effective concentration of Triton® X-100.

Although the applicant described the exposure scenario of the use of the IVD kits (ES-3) in the CSR, the applicant stated that it does not apply for an authorisation for the end-use with the argument that this use is potentially exempted from Authorisation based on ECHA Guidance on Scientific Research and Development (SR&D) and Product and Process Orientated Research and Development (PPORD). According to the applicant, the short service-life 'scenario' of the tests/kits in the CSRs has been included only for the traceability of the 4-tert-OPnEO.

RAC points out that this end-use is outside the scope of this authorisation since no specific application for this use has been presented (e.g. no CSR, AoA and SEA documents have been provided). Therefore, RAC has not evaluated the exposure scenario for end-users (ES-3) and consequently no reference to the end-user exposure scenario is made in this opinion document. Also, RAC has not evaluated if the conditions for the SR&D exemption have been met.

Initially, the applicant had estimated an amount of 976 kg 4-tert-OPnEO for the year 2019 to be used to calculate the releases for ES-1. However, the demand on molecular testing increased dramatically from the beginning of 2020 because of the COVID-19 pandemic and consequently also the consumption of 4-tert-OPnEO. The applicant stated that they currently foresee a consumption of 4-tert-OPnEO of (1,000-10,000, exact figure claimed confidential but known to RAC) kg for 2020, but that a precise forecast for the following years cannot be given due to the uncertainties linked with the unprecedented situation of the COVID-19 pandemic. Therefore, the applicant presented a hypothetical consumption of 6,500 kg per year, which could be achieved only considering maximum production rate with the existing facilities and no other limiting factors for production (plastic consumables, packaging, other reagents, etc).For ES-2, the maximum quantity of 4-tert-OPnEO during the 2015-2019 period was consumed in 2016, with 9.16 g. Since the forecasts for 2020 do not lead to higher amounts, the quantity consumed in 2016 is used in order to assess the worst-case environmental exposures under ES-2. This consumption is not impacted by COVID-19 crisis.

ES-1, Grenoble

Table 1: Contributing Scenarios presented in the Use-1 ES-1

Contributing scenario	ERC/PROC	Name of the contributing scenario
ECS1	ERC2	Releases
WCS 1	PROC0	Supply and storage
WCS 2	PROC9	Weighing
WCS 3	PROC5	Mixture-production of reagents
WCS 4	PROC9	Packaging
WCS 5	PROC0	Transfer
WCS 6	PROC9	Secondary packaging
WCS 7	PROC0	Distribution

1. Supply and storage

Triton® X-100 is stored in a locker located in the production area. Triton® X-100 bottles are never opened during this step.

2. Weighing

Varying quantities of are weighed in adapted glass beakers. Each weighing batch is covered with aluminium Triton® X-100 prior to any movement in the production area.

3. Mixture – Production of reagents

Production operations consist of a series of mixtures and dilution. The operations are performed by workers in glass flasks for small quantities (110 L) or carried out in enclosed equipment, such as large single use plastic bags for bigger quantities (liners – 1 080 L). Glass containers containing Triton®X-100 are emptied into bulk mixture containers and then rinsed with water two times. The rinsing water is directly added to the mixture.

4. *Packaging*

Liquid mixtures containing Triton® X-100 in a concentration between 1 % and 10 % (exact concentration claimed confidential) are packaged into small vials (12 mL) or bottles (1 L) using dispatching automatons, equipped with a removable drip tray to avoid spills.

5. *Transfer and 6. Secondary packaging*

Once closed, the vials are packaged in cardboard packs and bottles are dropped into larger boxes with retention insert. The vials are sent to a subcontractor for secondary packaging, then sent back to the site of Grenoble, remaining hermetically closed at all time.

7. Distribution

Cardboard packs, that contain nucleic acid extraction reagents are distributed to end-users while vials/bottles remain hermetically closed at all times.

ES-2, Grenoble

Table 2: Contributing Scenarios presented in the Use-1 ES-2

Contributing scenario	ERC [PROC]	Name of the contributing scenario
ECS1	ERC2	Releases
WCS 1	PROC0	Supply and storage
WCS 2	PROC5	Weighing-mixture (dilution+aliquoting)
WCS 3	PROC15	Quality control
WCS 4	PROC5	Weighing-mixture (dilution)
WCS 5	PROC9	Lyophilisation
WCS 6	PROC9	packaging
WCS 7	PROC15	Quality control
WCS 8	PROC0	Transfer
WCS 9	PROC9	Secondary packaging
WCS 10	PROC0	Distribution

1. Supply and storage

Intermediate raw material containing Triton® X-100 in a concentration below 1 % are supplied in 2-50 mL vials in dry ice and stored in a central low temperature chamber at -20 °C, awaiting quality control (see step 3 below). Advanced storage consists in freezers located in the production zone. Transfer between different areas is realized using a vial rack and a trolley. Vials are never opened during this step. Triton® X-100 is stored in a locker located in the production area. Triton® X-100 bottles are never opened during this step.

2. Weighing – Mixture – Dilution + Aliquoting

4-tert-OPnEO containing material is aliquoted into smaller plastic vials (< 2 mL), using an automated pipette under a biological safety cabinet. Vials are immediately closed. For the formulation of enzyme dilution buffers, varying quantities (< 2 g) of Triton® X-100 are weighed into a disposable plastic bottle with other reagents and after sufficient quantity to final volume repartitioned into aliquots which are immediately sealed. Vials are stored at -20 °C in the freezer before further use.

3. Quality control

Quality control on intermediate raw material containing Triton® X-100 in a concentration below 1 % consists in laboratory analysis of biological properties. It is realized in controlled conditions by trained personnel. The applicant considers this phase to be exempted from authorisation.

4. *Weighing-Mixture-Dilution*

Aliquots of 4-tert-OPnEO containing material are diluted with specific buffer also containing 4-tert-OPnEO using plastic bottles of 1-2 L and under a biological safety cabinet. Final 4-tert-OPnEO concentrations are below 1 %w.w.

5. *Lyophilisation and 6. Packaging*

Triton® X-100 containing mixtures are lyophilised and packaged into small vials (2 mL). Containers are connected to the pump of the automated system. 50 µL drops are formed, they immediately fall into liquid nitrogen freezing into beads. Beads are then sorted on a sieve and

lyophilised, where the remaining solution is withdrawn from the beads. Beads are then immediately packaged in small vials.

7. *Quality control*

Quality control on final material containing Triton® X-100 consists in laboratory analysis of biological and analytical properties. It is realized in controlled conditions by trained staff.

8. *Transfer and 9. Secondary packaging*

Vials are labelled and packaged into bags and cardboard boxes and temporarily stored at room temperature in a logistic area. Vials are sent to a subcontractor for secondary packaging, then sent back to the site of Grenoble, remaining hermetically closed at all time. Vials are never opened during these steps.

10. *Distribution*

Cardboard IVD packs that contain kits are distributed to end-users while vials remain hermetically closed at all time.

0.2. Key functions and properties provided by the Annex XIV substance

4-tert-OPnEO main functionalities include detergency in mild conditions, ability to disrupt cellular membranes and then, to solubilize and to stabilize proteins or enzymes and concomitant pathogen inactivation properties according to the kind of cellular materials to be diagnosed.

0.3. Type(s) of product(s) made with Annex XIV substance and market sector(s)

bioMérieux products are at the end used by professionals in hospitals or laboratories to carry out *in vitro* diagnostics. The use of 4-tert-OPnEO concerns two NucliSens® in vitro reagents ranges.

NucliSens® extraction range:
Four different buffer solutions (extraction and lysis buffers) involved in the preparation of nucleic acids by extraction from biological specimens (e.g. human fluids, veterinary or food samples) further used in different in vitro diagnostic (IVD) and non-IVD applications. These buffer solutions are used on EMAG™, easyMAG®, miniMAG™ and eGENE-UP® extraction platforms. EMAG™, easyMAG® and miniMAG™ are dedicated to clinical use, while eGENE-UP® is used in the industrial sector (food, pharmaceutical, veterinary, cosmetic). The applicant also describes that, due to prevailing market conditions, a transition of assays away from semi-automated systems (using standalone extraction platforms such as EMAG™ and easyMAG®) to fully integrated automated platforms is foreseen in the coming years.

From the year 2020, buffer solutions are also used in the easyMAG® and EMAG™ systems in the frontline of the COVID-19 molecular testing efforts providing essential sample preparation needs initially in front of local laboratory-produced laboratory developed tests (LDT) and then been further applied to commercial SARS-CoV-2 molecular assays. Recently bioMérieux's own SARS-CoV-2 assay was launched.

NucliSens® easyQ®:
One enzymatic reagent used in the process of amplification of ribonucleic acid (RNA), in HIV diagnosis and follow-up.

1. Operational Conditions and Risk Management Measures

1.1. Environment

The applicant presented two contributing exposure scenarios:

- ES-1: Production of reagents for Total Nucleid Acid Extraction at Grenoble, France (ERC2: Formulation into mixture).
- ES-2: Production of reagents for clinical IVD testing applications at Grenoble, France (ERC2: Formulation into mixture)

A summary of the operational conditions (OCs) and risk management measures (RMMs) in the environmental contributing scenarios is provided below. The detailed conditions of use are available from sections 9.2 and 9.3 of the CSR. No worker contributing scenarios are presented, as the scope of the CSR is limited on the environmental risk of 4-tert-OPnEO.

Table 3: Operational conditions

	ES-1	**ES-2**
Volume used per year	6 500 kg	0.00916 kg
Number of days of release per year	240	60
Concentration of 4-tert-OPnEO	Triton™ X-100: ≥ 99 %-≤ 100 %	Triton™ X-100: < 1 % in the commercial enzyme
Daily release of 4-tert-OPnEO	1.2×10^{-2} kg/day (monitoring)	3.05×10^{-6} kg/day (ERC2)

According to the applicant the following RMMs are implemented:

Technical and organisational conditions and measures

- The installations located in Grenoble are subject to the technical requirements of the corresponding prefectoral order ("Arrêté prefectoral") which concern among others prevention of water and air pollution and waste management.
- The production steps are generally carried out under clean room conditions of ISO-8 classified cleanroom (according to the ISO 14644-1 Standard 1). Only rooms dedicated to the filling of products are classified as ISO 5.
- Supervision of operators involved.
- The workers are trained to use mixtures containing the substance.
- Documents related to risk prevention and general maintenance of facilities and equipment are available for Local Authorities in charge of compliance checks.
- Yearly cleaning of the wastewater buffer pit at the wastewater output of the site as measurements showed that this pit was a source of OPnEO contamination, (see section 2.1).

Waste management

- Monitoring program of degradation products using ISO 18857-2 method (quarterly measurements) in its water discharges going to STP. This program has been implemented in 2018 and will be continued during the review period.
- The applicant's production plants are built on concrete retention areas to avoid any spillage into the environment. The applicant has implemented emergency plans in case of spills.

- Applicant has implemented emergency plans in case of spills (e.g. use of absorbent material, how to collect and dispose of the spilled liquid).
- Waste management at the site of Grenoble is set by a specific procedure describing specific instructions for chemical waste.
- All chemical and infectious wastes are collected by a certified provider for incineration.
- Solid waste: All non-reusable devices used in the different production steps which has been in contact with 4-tert-OPnEO are collected and disposed of for incineration (e.g. empty packages, expired products cotton wool items for cleaning spills, plastic vials, pipette tips, single use tubing and plastic bags, cleaning material).
- Liquid waste: Contaminated effluents from production are collected in specific 1 L or 10 L containers and identified as dangerous liquid waste (e.g. solution on the drip tray) The containers are stored in a dedicated area before collection for incineration.
- The incineration of waste (liquid and solid) containing 4-tert-OPnEO is performed by the certified waste operator and is traceable by regulatory documents (e.g. waste tracking slips).
- Glass containers used during the mixing are rinsed two times with water (rinsing water is added to the mixture) before sending to the glassware laundry. Wastewater coming from the glassware laundry (glass containers used for weighing, and mixing, drip trays, repartition pipes) is not collected for treatment and therefore identified as potential releases of 4-tert-OPnEO.

Table 4: Environmental RMMs - summary

Compartment	RMM	Stated Effectiveness
Air	Mostly closed process.	No emission to air is expected due low vapour pressure of the substance and RMM in place.
Water	Collection and incineration of contaminated effluents and solid waste.	For incineration of solid and liquid wastes a 100 % efficiency is assumed. Wastewater coming from the washing of glassware is not collected, therefore potential release.
Soil	Well controlled and clean environment.	No direct release to soil at site expected.

1.2. Discussion on OCs and RMMs and relevant shortcomings or uncertainties

The description of the OCs and RMMs is clear for both ES-1 and ES-2.

The applicant pointed out that all OCs and RMMs remain the same and therefore have not been changed due to the recent high production increase and consumption of 4-tert-OPnEO as a consequence of the increased demand for COVID-19 test devices. Also the waste management strategy remains unchanged although a more frequent collection of wastes by the certified service provider takes place.

Since all single use devices, which had been in contact with 4-tert-OPnEO, are collected and disposed of as waste for incineration and the relevant wastewater is collected for incineration, no relevant shortcomings to the OCs and RMMs have been identified.

RAC noticed that, reusable devices used in several process steps and which have been in contact with 4-tert-OPnEO, are sent to the glassware laundry which discharges effluents into

the STP.

The applicant indicated that, at the moment, collection of the effluents from glassware laundries for incineration is not being considered as it represents huge amounts of water in comparison to the expected low concentration of 4-tert-OPnEO, leading to technical (e.g. lack of space, creation of retention zones complicated by the presence of large gas pipelines) and economic constraints (e.g. addition of collection tanks, modification of the laundry evacuation network).

The applicant informed that they are currently implementing an action plan to decrease releases of 4-tert-OPnEO.This was triggered by the high monitoring results for OP from December 2018 (when the quarterly monitoring campaign was first implemented, see also section 2.1). After researching possible sources of octylphenols in the effluents released to the sewerage[7], the applicant found that the wastewater buffer pit (at the output of the site, located just upstream where sampling is being performed during the monitoring campaigns) accumulated 4-tert-OPnEO residues. Therefore, the applicant decided to annually clean the pit during the review period.

RAC notes that the applicant has assessed the technical viability of the additional risk management measures and/or operational conditions needed to ensure a complete collection of the effluents and that they (the applicant) conclude that the implementation of such measures has technical and organizational constraints.

The applicant informed that they currently are assessing the replacement of glassware by single use items for the production of several buffer solutions

The applicant pointed out that the efficiency of RMM implemented on-site is constantly verified in order to maintain to a minimum or even decrease any release of the substance and, therefore, its environmental impact.

1.3. Conclusions on OCs and RMMs

Overall conclusion

OCs and RMMs in the ES are appropriate and effective in limiting the risk.

Are the operational conditions and risk management measures appropriate[8] and effective[9] in limiting the risk for workers, consumers, humans via environment and/or environment?

Workers	☐Yes	☐No	☒Not relevant
Humans via Environment	☐Yes	☐No	☒Not relevant
Environment	☒Yes	☐No	☐Not relevant

Minor concerns in the RMMs lead to recommendations for the review report presented in section 9.

[7] Used detergents of cleaning and maintenance works, were disregarded as a potential source of 4-tert-OPnEO contamination, since no phenolic compounds, were detected by analysing these detergents.
[8] 'Appropriateness' – relates to the following of the principles of the hierarchy of controls in application of RMMs and compliance with the relevant legislation.
[9] 'Effectiveness' – evaluation of the degree to which the RMM is successful in producing the desired effect – exposure / emissions reduction, taking into account for example proper installation, maintenance, procedures and relevant training provided.

2. Exposure assessment

2.1. Environmental emissions

Water

Solid and liquid waste, with the exception of the wastewater from the glassware laundry, is collected for incineration. Therefore, the environmental release estimate presented by the applicant is based on the residual release from washing water of reusable devices (e.g. glassware, pipes).

The applicant informed that since December 2018 quarterly monitoring have been taken place of the wastewater discharged into the sewage system, analysing the parent substance 4-tert-OPnEO, as well as 4-OP, OP1EO and OP2EO according to ISO 18857-2 standard method[10]. The analyses have been performed by an accredited laboratory. The results are presented in Table 5.

Table 5: Measurements of wastewater at Grenoble site from December 2018 to July 2020

	12/2018	05/2019	07/2019	10/2019	02/2020	05/2020	07/2020
4-tert-OPnEO (µg/L)	355	< 0.1	< 0.1	< 0.1	NA	8.2	280
4-OP (µg/L)	< 10.05	16	0.3	2	2.5	< 0.1	< 0.1
OP1EO (µg/L)	542	< 0.1	< 0.1	< 0.1	< 0.1	25.9	7.8
OP2EO (µg/L)	54	5.3	7.2	3	0.8	27.6	< 2.5
Sum OP (µg/L)	961	21.3	7.5	5	3.3	61.7	290.4
Daily flow rate to STP (m^3/day)	10	3.3	4.0	7.3	15	8	17
Daily releases (g/day)	9.69	0.070	0.030	0.037	0.050	0.49	4.94
Monthly releases (kg/month) (1)	0.194	0.00141	0.00060	0.00073	0.00099	0.00987	0.0987
Annual tonnage (kg/year)(1)	877	563	563	563	not available	not available	not available
Monthly tonnage (kg/month)(1)	73	47	47	47	47-470	47-470	47-470
Release factor (%)	0.265	0.0030	0.0013	0.0016	0.0014	0.0036	**0.032**

(1): The applicant considered 20 emission days per month and 240 emissions days per year

The applicant stated that the wastewater buffer pit was the main source of contamination of 4-tert-OPnEO and therefore it is thought to be responsible for the relatively high unexpected concentrations found in the first monitoring campaign (December 2018). Following the cleaning of the pit in April 2019, the measured concentrations remained at a low level until

[10] Limit of detection: 20.10 µg/L for 4-tert-OPnEO and OP2EO; 10.05 µg/L for 4-OP and OP1EO;

July 2020. For this reason, the liquid waste pit will be cleaned yearly with the next cleaning planned for September 2020.

For ES-1 the release factor was calculated based on the monitoring campaigns (sum of the parent substance and the three measured degradation components), the daily flow rate of wastewater discharged into the sewage system and the monthly amount used[11] (see Table 5).

The release factor in the original application for authorisation (0.29 %) was based on a very limited monitoring data set. The current release factor (0.032 %), which is significantly smaller than the original one, is based on a much more comprehensive data set (as it can be seen in Table 5), therefore the releases have not increased despite the volume increase due to Covid-19 activities.

The applicant further elaborated that the release factor remained stable at a low level (average 0.002 %) until May 2020, although the consumption rate of 4-tert-OPnEO has been increased by a factor of (1-10) compared with the years 2018 and 2019. The release factor increased in July 2020 (as pointed out earlier), presumably due to the accumulation of 4-tert-OPnEO in the waste pit. The applicant stated that actions are taken to restore the release factor to the levels observed in 2019.

For the calculation of the yearly releases the applicant used the highest release factor of 0.032 %, as a worst-case situation, since it represents a high production level, which according to the applicant, is currently stabilising.

Taken into account the maximum foreseen used tonnage during the review period (6 500 kg) an annual release of 2.08 kg 4-tert-OPnEO/year is obtained which corresponds to a daily release of 0.0087 kg 4-tert-OPnEO/day.

For ES-2 the default release fraction of 2 % to wastewater from ERC2 was used for the annual quantity used by the applicant (maximum 9.16 g/year). Number of emission dates have been revised to 60 days/year.

Air

The applicant considered that release to air is negligible taking into account the activities performed and the substance handled.

Soil

The applicant considered that release to soil is negligible taking into account the activities performed and the substance handled.

Table 6: Summary of environmental emissions

Release route	**Release factor**	**Release per year** (kilograms)	**Release estimation method and details**
ES-1 Water	0.032 %	2.08	Based on monitoring.
ES-2 Water	2 %	0.000183	Based on default release fraction from ERC2.

[11] The calculation has been performed by month to enable the comparison as the annual tonnage for 2020 is not known yet.

2.2. Discussion of the information provided and any relevant shortcomings or uncertainties related to exposure assessment

Environment

The potential for release is reduced as a result of the use of 4-tert-OPnEO in mainly closed systems and incineration of solid and key liquid wastes. RAC considers that the methodology for assessing the exposure from residual releases to water is appropriate.

The calculated release estimates are based on site-specific input parameters, representing worst case scenarios. All parameters are transparently reported and adequately justified. The estimates can be considered to be representative and are not likely to underestimate exposure.

RAC agrees with the applicant's conclusion that the measurement data of December 2018 which were taken before cleaning the wastewater buffer pit, are not representative for the current situation, since subsequent measurements have been significant lower.

The applicant pointed out that quarterly monitoring campaigns will be continued during the review period and based on the evolution of the outcomes, they will continuously seek to apply the most efficient management to reduce the releases of 4-tert-OPnEO to wastewater to a level as low as technically possible during the review period requested.

The applicant acknowledged that the actual monitoring method may lead to uncertainties about the real concentrations of the Triton X-100 releases on sites (complex mixture with an average of 9.5 ethoxylate units) since the normalized method (ISO1887:2) is limited to the detection of alkylphenols ethoxylates up to two ethoxylate units.

The use of a new and more accurate method is envisaged by the applicant. This method will allow the measurement of all related ethoxylated compounds as a sum of octylphenols. The applicant commits to switch on this novel and relevant method when public information will be available.

Therefore, RAC points out that a quarterly monitoring program, which the applicant committed to perform, will give a better insight of the releases to the water compartment and will corroborate the effectiveness of the RMMs and OCs in place.

RAC acknowledges that for the release calculations a conservative approach has been used (the highest release factor has been taken forward), although uncertainties remain about the impact on the releases of a further increase of the annual used amount of 4-tert-OPnEO as this is mainly affected by the surge in demand due to the COVID-19 crisis.

As a result of the relatively low vapour pressure of 4-OPE[12] and the level of containment in the processes (largely in closed systems), RAC concurs that releases to air are expected to be negligible. Similarly, RAC agrees that direct releases to soil are not likely.

2.3. Conclusions on exposure assessment

RAC considers on balance that the release estimates provided by the applicant are appropriate.

RAC notes that some shortcomings remain in the assessment related to the analytical method available to detect alkylphenols ethoxylates and the impact that a potential increase of the amount 4-tert-OPnEO used will have on the releases. RAC considers that the actions proposed

[12] The applicant reports that 4-OPE has a vapour pressure of 0.01 hPa at 20 °C (0.001 kPa at 20 °C). As the vapour pressure is below 0.01 kPa, 4-OPE is not a 'volatile organic compound' as defined by the Industrial Emissions Directive (Directive 2010/75/EU): "'volatile organic compound' means any organic compound as well as the fraction of creosote, having at 293.15 K a vapour pressure of 0.01 kPa or more, or having a corresponding volatility under the particular conditions of use".

by the applicant related to the implementation of monitoring of releases according to adequate analytical methods (as soon as they become available) and to take the necessary actions to restore the release factor to the levels observed in 2019, are appropriate to address the uncertainties identified.

3. Risk characterisation

The human health assessment (Man via environment, workers and consumers) is not considered according to: (EC) No 1907/2006 (REACH).

The applicant has treated 4-tert-OPnEO as a non-threshold substance. This approach is in line with RAC's paper *"Risk-related considerations in applications for authorisation for endocrine disrupting substances for the environment, specifically OPnEO and NPnEO"* adopted at RAC-43 and as concluded by RAC at its 50th meeting that a reliable threshold for endocrine disrupting effects could not be determined based on currently available data

RAC did not evaluate the predicted environmental concentrations (PECs) provided by the applicants since 4-tert-OPnEO is treated as a non-threshold substance for its endocrine disrupting properties for the environment and therefore no appropriate PNECs are available for comparison, nor is the Water Framework Directive EQS value considered to be suitable for this purpose.

Based on the OCs & RMMs in the ES, the total amount of 4-tert-OPnEO used per year, the collection and disposal of solid waste and the relevant wastewater for incineration, RAC is of the view that the applicant has demonstrated that releases to environmental compartments have been prevented or minimised as far as technically and practically possible (with the view to minimising the likelihood of adverse effects).

The use applied for may result in emissions of 2.08 kg/year based on the monitoring data and the maximum foreseen amount used during the review period (6 500 kg/year) of the substance to the environment.

4. Analysis of Alternatives and substitution plan[13]

What is the amount of substance that the applicant uses per year for the use applied for?

6 500 kg/year

The use of 4-tert-OPnEO under the use applied for concerns the products described in section 0.3 (see summary in Table 7 below):

[13] The judgment of the ECJ Case T-837/16 Sweden v Commission stated that the applicant has to submit a substitution plan if alternatives are available in general. The Commission is currently preparing the criteria, derived from the judgment for establishing when an alternative is available in general. Once these are prepared this opinion format will be amended accordingly. The European Commission informed the REACH Committee in 9-10 July 2019 of its preliminary views on the criteria. In that note that Commission considered that the criteria defining a 'suitable alternative' would imply that it was i) *safer* and ii) *suitable*. Suitability would not mean it to be "*in abstracto"* or "*in laboratory or exceptional conditions*" but it should be "*technically and economically feasible in the EU*" and "*available, from the point of view of production capacities of the substance or feasibility of the technology, and legal and factual conditions for placing on the market*".

Table 7: Products concerned by the use applied for

REAGENT REFERENCES	REAGENT/KIT NAME CONTAINING 4-tert-OPnEO	SYSTEM	PROCESS
280130	NucliSens® Extraction Buffer 1-4x1L	**NucliSens® easyMAG® EMAG™ eGENE-UP®**	**Extraction**
280134	NucliSens® Lysis Buffer 4x1L		
200292	NucliSens® Lysis Buffer 2 mL		
200293	NucliSens® Magnetic Extraction Reagents Kit Wash Buffer 1 (ref. 60085067)[21]	**NucliSens® miniMAG™**	
285033	NucliSens® easyQ® HIV-1 v2.0 48 tests kit - Containing ENZII reagent (ref. 60085713)[22]	**NucliSens® easyQ®**	**Amplification**

4-tert-OPnEO is one of the most popular non-ionic surfactant used for disrupting cells. It provides key properties such as sensitivity, specificity, reproducibility and accuracy which are of critical importance. The main functional properties sought-after with 4-tert-OPnEO under the use applied for include:

- Being a non-ionic surfactant;
- Being a mild detergent;
- In the extraction processes solubilize and facilitate the removal of numerous undesirable molecules which could disrupt this amplification process;
- Having an HLB (hydrophilic-lipophilic balance) value between 13 and 15 in order to stabilise protein structures.

4.1. Summary of the Analysis of Alternatives and substitution plan by the applicant and of the comments received during the consultation and other information available

The applicant carried out an analysis of alternatives only for the use of 4-tert-OPnEO in NucliSens® extraction reagents (i.e. four different extraction and lysis buffers), while no such analysis was presented for the NucliSens® easyQ® HIV-1 reagent (i.e. one amplification reagent). This is because the applicant does not pursue substitution for the amplification reagent due to the planned discontinuation of production of NucliSens® easyQ® HIV-1 products by not long after the sunset date (certainly a much shorter period of time than the requested review period). The applicant listed a number of reasons for discontinuation, including costs of developing an alternative, non-compliance of the relevant equipment (NucliSens® easyQ® system) with the RoHS 2 directive, as well as competitiveness considerations. The applicant further noted, in a response to a SEAC question, that the use of 4-tert-OPnEO concerning the amplification reagent is considered insignificant (on average 0.00549 kg/year in the 2015-2018 period) relative to the quantities of 4-tert-OPnEO used in the production of extraction reagents (on average 874 kg/year in the 2015-2018 period).

Concerning the use of 4-tert-OPnEO in NucliSens® extraction reagents, an initial screening of

potential alternatives led to the identification of six non-ionic detergents (list claimed confidential by the applicant). Non-ionic detergents were selected because of their non-denaturing properties, meaning that the residual presence of the detergent in the nucleic acid purification eluates should not impact the activity of the enzymes used for nucleic acid amplification. The selection of these six short-listed alternatives was based on literature review aiming to identify detergents with physico-chemical properties – critical micellar concentration, water solubility, cloud point, foam height, and hydrophilic-lipophilic balance (HLB) – close to those of Triton™ X-100. In addition a regulatory study was made to remove all the substances which were very toxic (e.g. CMR) or which would likely, in the future, end up in the Annex XIV Candidate List.

Performances of the reagents obtained using the short-listed alternatives have then been compared to those of a reference solution produced with 4-tert-OPnEO. The influence of the surfactant was firstly studied and then, in a second part, different specimens (whole blood, plasma, stool) and applications (PCR, RT-PCR, NASBA, sequencing, dosage of DNA/RNA recovery/purity) were tested on various nucleic acids targets. As a result, the potential list of alternatives was reduced to three substances. According to the applicant, these three alternatives have yet to be further investigated, implemented and validated.

A comment was received from a third party (Health Care without Harm Europe) in the consultation, proposing a number of potential alternatives. The applicant addressed this comment by responding that some of their short-listed alternatives were part of the potential solutions identified by the third party in its list of alternative detergents and surfactants. The applicant also added that after checking the suggested substances by the third party, all of them have a suspicion of toxicity to aquatic life activity based on the ECHA database, notably at a long-term scale. To date, little information is available concerning the potential risks related to these molecules and the applicant considers that it would be counterproductive and contrary to the REACH regulation to move towards an alternative that might be listed as SVHC in the medium to long term. In any case, the applicant stated that it will take into account the potential alternatives available on the market.

4.2. Risk reduction capacity of the alternatives

Would the implementation of the short-listed alternative(s) lead to an overall reduction of risks?

☐Yes

☐No

☒Not applicable

SEAC concluded that currently there are no technically and economically feasible alternatives available for the applicant with the same function and similar level of performance. Therefore, RAC did not evaluate the potential risk of alternatives.

4.3. Availability and technical and economic feasibility of alternatives for the applicant

Are there alternatives with the same function and similar level of performance that are technically and economically feasible to the applicant before the Sunset Date?

☐Yes ☒No

SEAC's evaluation/view on the availability and technical and economic feasibility of alternatives for the applicant

Based on information provided by the applicant, SEAC can agree that there is no technically feasible alternative available by the sunset date. Currently the applicant has further narrowed down the initial list of six short-listed alternatives to three. These candidates will have to be further tested to ensure that all the requirements for substitutes are met. The battery of tests needed to be carried out are:

- Stability study at low (2 °C) and high (30 °C) temperatures, on three R&D lots;
- Tests on industry applications matrices (human and veterinary food);
- Tests on industry instrument (eGENE-UP® system);
- Test on other important matrices (respiratory, urine, CSF, bone marrow, etc.).

4.4. Substitution activities/plan

Has the applicant submitted a substitution plan?

☒Yes ☐No

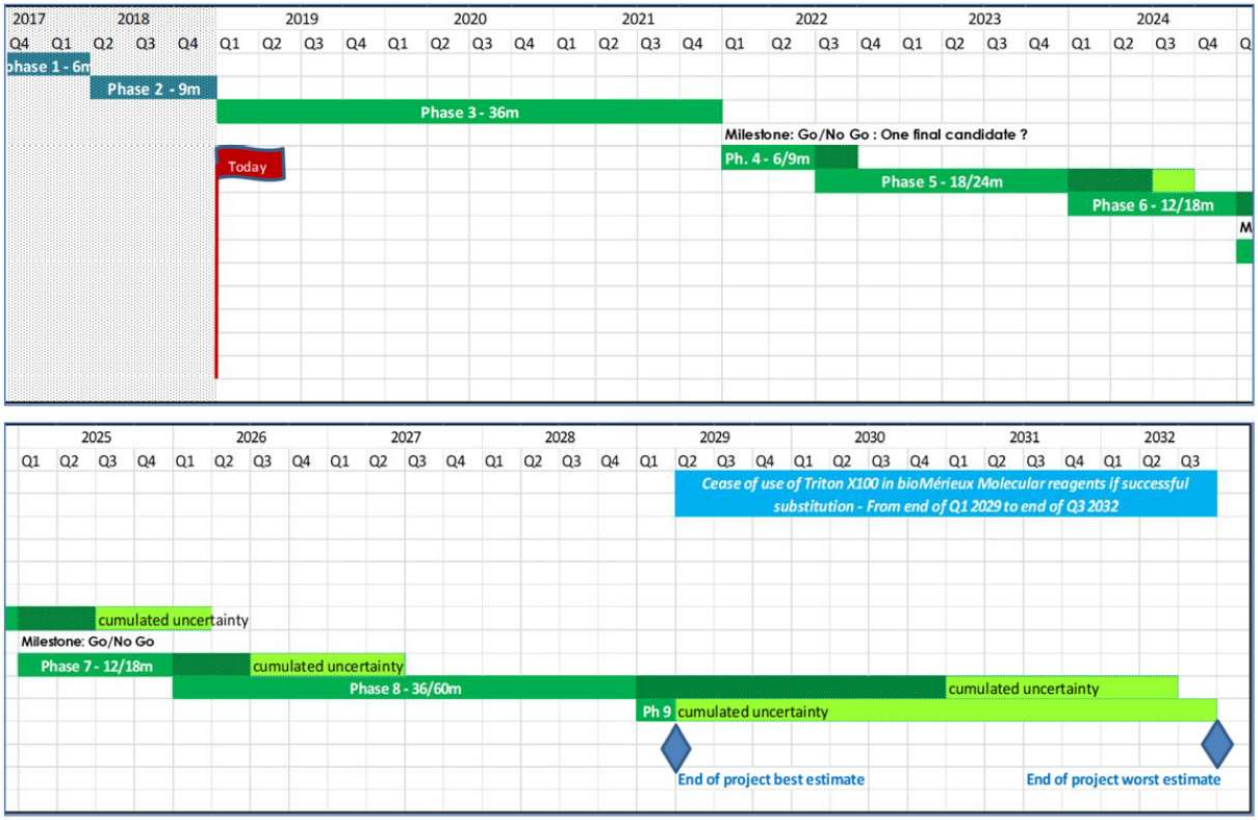
If yes, is the substitution plan credible and consistent with the analysis of alternatives and the socio-economic analysis?

☒Yes ☐No

SEAC's evaluation/view on the substitution activities/plan

The applicant is already engaged in a substitution programme. The applicant claims that the short-listed alternatives will have to be further assessed for technical, normative and customer functional requirements. The applicant is working on a substitution initiative consisting of several different steps, each with a defined schedule for implementation as illustrated in Figure 1 below.

Figure 1: Substitution timeline



The substitution initiative is divided in nine phases, of which the first two (Phase 1: Screening of potential alternatives and Phase 2: First assessment of substitution in extraction reagents) have already been performed. The remaining phases will include the following main steps:

- Phase 3: Finalisation of substitution feasibility (concentration and reaction conditions, stability studies) on a selected alternative, only if this step is successful other phases will follow. The first stability evaluation is expected to occur within 24 months and the overall stage is expected to have a cumulative duration of 36 months.
- Phase 4: Creation of production documentation for reformulated reagents and production of test batches (6-9 months).
- Phase 5: Industrial performances verification on various clinical and industrial reagents using reformulated reagents (18-24 months).
- Phase 6: Clinical performances verification of bioMérieux assays using reformulated reagents (12-18 months).
- Phase 7: Launch of reformulated reagents and international registration, production of commercial batches for customers (12-18 months).
- Phase 8: Validation by customers of their applications by comparison with reference reagents, while performing routine tests with the reference reagents (36-60 months).
- Phase 9: End of life-cycle of Triton™ X-100 containing reagents range (3 months).

In response to SEAC's questions, the applicant elaborated further on the complexities of the substitution process. In particular, the applicant argued that:

- Their extraction systems are used for a broad range of specimens and applications (assays or analytical methods) which can be combined into a single run with a single set of on-board reagents. Only one alternative will be selected for all applications

affecting all user applications.

- A complete performance revalidation of the reagents and associated equipment on a large and highly diverse range of specimens and applications must be done not only internally but also externally by every customers for all their IVD and non-IVD applications.
- Regulatory requirements: Substitution of the detergent will require new registrations.

The applicant concluded that a 12-year review period would be needed to attain the full substitution of 4-tert-OPnEO.

The applicant stated that the implementation of the substitution plan will be monitored through regular meetings with representatives of the relevant units involved in the substitution initiative, in particular production and R&D. Once an alternative has passed the R&D stage, its implementation at the industrial scale will be monitored via an internal change management procedure. The progress made in the implementation of the different phases as well as any difficulties encountered will be synthesised in an annual summary report.

SEAC finds the substitution initiative credible, with well described phases and timelines for completion assigned to each of them.

4.5. Conclusions on the analysis of alternatives

SEAC concludes that the analysis of alternatives is sufficiently detailed to conclude on the technical and economic feasibility of the alternatives and the derived review period requested by the applicant. The applicant described the use applied for in detail and the requirements associated with a valid alternative. The applicant presented in its analysis of alternative a substitution initiative consisting of nine different phases of which two are already fulfilled (Phase 1: Screening of potential alternatives and Phase 2: First assessment of substitution in extraction agents). Following phase 2, the short-listed alternatives will be further tested, in particular in key customer applications. The applicant has listed each phase in the substitution initiative and its timetable for completion as well as the expected outcome. In response to SEAC's request, the applicant elaborated on the rationale behind the key stages of the substitution initiative as well as on how uncertainties and factors, that may hinder or accelerate the substitution, have been addressed and taken into consideration in the timetable for substitution.

By the sunset date there are no alternatives available with the same function and similar level of performance that are safer and technically and/or economically feasible for the applicant. The substitution plan is credible and consistent with the analysis of alternatives and the socio-economic analysis.

5. Benefits and risks of continued use

Has the applicant adequately assessed the benefits and the risks of continued use?

☒ Yes

☐ No

5.1. Human health and environmental impacts of continued use

According to the applicant, all contaminated solid waste is collected and incinerated by a

certified provider. Consequently, no releases of 4-tert-OPnEO to the environment are expected by this route. For liquid waste, releases could potentially arise from washing non-disposable glassware and repartition pipes contaminated with diluted 4-tert-OPnEO solution. Amongst the liquid releases, only those coming from laundry and glassware washing are discharged into sewage. They are then treated through the local wastewater treatment system. The applicant claims that releases are expected to be extremely low (2.08 kg/year 4-tert-OPnEO according to monitoring data) and should not contribute to an eventual contamination of the immediate environment. The applicant also states that it is committed to continue seeking to reduce the 4-tert-OPnEO releases to wastewater to a level as low as technically possible during the review period.

The Isère River region, near the applicant's site, and the Rhône-Méditerranée basin show that pollution is mainly related to PAHs, pesticides and hydrocarbon releases. While octylphenols are part of this global pollution, in comparison with other substances, they are rarely quantified or measured in amounts considered insignificant, according to the applicant.

4-tert-OPnEO was included on Annex XIV of REACH due to the environmental impacts of its degradation products. As a result, impacts on human health are not included in the context of this application.

5.2. Benefits of continued use

Non-use scenario

According to the applicant, the most likely non-use scenario for both NucliSens® extraction and lysis buffers as well as the NucliSens® easyQ® HIV-1 reagent is the cessation of production of NucliSens® extraction products and NucliSens® easyQ® HIV-1 products. In the case of NucliSens® extraction and lysis buffers, the applicant briefly discusses alternative non-use scenarios, including performance degradation, relocation or sub-contracting outside the EU, but dismisses these on the basis of the qualification process for the products, the demanding requirements on product performance which require substantial financial investment and high level of staff know-how. The applicant explains that there is a significant level of internal expertise at the Grenoble site, without which it is likely that product performance would be reduced. This may, in turn, generate subsequent costs, regulatory action and possibly withdrawal of the product from the market. Moreover, the applicant fears that the loss of internal expertise would put its intellectual property at risk.

These non-use scenarios are not considered for the NucliSens® easyQ® HIV-1 reagent as the applicant states that they are not economically or technically relevant given that the NucliSens® easyQ® product range will be discontinued.

What is likely to happen to the use of the substance if an authorisation was not granted?

- the use would cease altogether
- the use would be substituted by market actors operating inside the EU
- the use would be taken up by market actors operating outside the EU

What is likely to happen to jobs in the European Union if an authorisation was refused?

- 8.6 jobs would be lost

Socio-economic impacts of continued use

The applicant assesses three main categories of impacts: economic impacts on the applicant and its supply chain, health impacts on patients and customers, and an employment-related impact on the applicant's employees.

Economic impacts

In terms of economic benefits for the applicant, granting an authorisation would avoid lost profits as a direct result of being able to continue manufacturing the NucliSens® extraction and easyQ® HIV-1 product ranges.

Initially, the applicant estimated the economic impact in terms of lost revenue over the 12-year review period applied for. Assuming a constant positive annual growth rate (based on forecasted growth in the general IVD market) and using a discount rate of 4 % for each product range, the applicant estimated a loss in revenues in the range of €100 million to €1 billion (present value in 2019) in the non-use scenario. As the applicant stated that a decline in the standalone extraction business was expected due to prevailing market conditions, SEAC questioned the assumption of a constant positive annual growth rate. In response, the applicant revised its revenue forecasts downwards but found that it was still in the €100 million to €1 billion range over the review period.

In the comments on the draft opinion, the applicant explains that demand for 4-tert-OPnEO-containing extraction buffers has increased dramatically due to the COVID-19 crisis. As a result, the applicant's market outlook has changed and bioMérieux expects the revenues related to its extraction business to be considerably higher compared to the revised revenue forecast that was provided in response to the SEAC question. According to the forecast provided in the comments on the draft opinion, the applicant estimates revenue losses over the requested review period in the range of €100 million to €1.5 billion (present value in 2019; discounted at 4 %). The applicant adds, however, that due to the uncertainties related to the COVID-19 crisis, this estimate does not represent a precise forecast.

SEAC notes that revenue is not a good indicator of benefits to society and that the focus should instead be on profit because this recognises that both revenues and costs can vary in response to changes in output. The applicant, consequently, provided supplementary information indicating that between 2015 and 2017, net profits have represented 10-15 % of annual revenues (this profit rate has been confirmed by bioMérieux in the comments on the draft opinion). Assuming that this profit rate remains constant over the requested review period, and applying it to the applicant's estimate of lost revenues as provided in the comments on the draft opinion, profit losses can be estimated in the range of €10-225 million over the requested review period.

In addition to the quantified impacts, the applicant discussed further economic impacts qualitatively. In the case of the NucliSens® extraction product range, this constitutes a key element of the applicant's product portfolio, without which the applicant would be prevented from participating in calls for tender. The applicant argues that the loss of NucliSens® extraction products would have a significant knock-on effect on sales of other products in bioMérieux's portfolio with the result that several markets would be closed for 3-10 years, depending on the duration of tenders. The applicant believes that in order to avoid potential

supply disruptions, some customers would be driven to find alternatives earlier than planned and the pace at which profit losses would be incurred would be difficult for the company to absorb.

The applicant describes further costs that the company would face in a case where authorisation was not granted. One such cost arises from the earlier than anticipated end of life of reagents and associated instruments (estimated at €48.5 million). As these are considered sunk costs by the applicant, they are not considered further by SEAC. Additional costs are discussed qualitatively and relate to penalties that would be incurred as a result of range discontinuation such as fines or lawsuits for non-compliance with contractual obligations.

In response to SEAC questioning regarding the ability of competitors to supply the market before the end of the requested review period, thus, partially compensating the applicant's profit losses from a societal perspective, the applicant states that it is not aware of its competitors' strategies or production capacities. The consultation also did not indicate that there are suppliers in a position to supply the market using reagents that are not subject to authorisation under REACH. There are competitors based, or with manufacturing sites, outside the EU that could potentially supply the market but in such a case customers could face considerable costs related to purchasing new equipment, training personnel and re-validating applications. It is also not clear as of yet whether potential alternatives would have the same performance characteristics as bioMérieux's platforms. SEAC considers it plausible that in the absence of authorisation, there would be a disruption to supply as well as a loss in societal profits in the short to medium term.

Health impacts

The applicant's products concerned by the use applied for provide significant support in the diagnosis, follow-up and exclusion of numerous pathologies, which are applied in various medical specialities, on a global scale. Any supply disruption to bioMérieux's NucliSens® extraction products would have an impact on hospitals and laboratories that will ultimately be passed to patients. In particular, there would be a disruption in the earlier detection of the pathologies, reducing the patient's chance of survival and potentially increasing the costs of treatment and hospitalisation. In the comments on the draft opinion, the applicant also emphasises the essential role its extraction products play in testing efforts related to COVID-19.

There would be a cost to hospitals and laboratories of replacing equipment, training personnel and revalidating assays using a new extraction system. In some jurisdictions, there would be costs associated with resubmission/registration with regulatory bodies. Another impediment to changing suppliers for IVD services lies in the fact that hospitals and laboratories usually have global contracts to optimise costs. A break in supply would result in the need to reissue an invitation to tender for all tests (which may not be possible if the alternative supplier does not offer a comparable test portfolio or allow ad hoc use of their system).

Data provided by the applicant shows that between 1 and 10 million extractions were commercialised in 2018 using NucliSens® extraction products. According to bioMérieux, it can be considered that each extraction results in approximately 1.8 diagnostic tests. Similarly, between 100 thousand and 1 million easyQ® HIV-1 tests were used to monitor the HIV-1 viral load in 2018.

bioMérieux also offers a full range of industrial microbiological diagnostics tests in other sectors. For example, it provides for the detection of pathogenic microorganisms in the food safety industry, it facilitates sterility control of drugs, environments and products in the cosmetics and pharmaceuticals sectors and it also develops extraction and detection solutions for veterinary products. As is the case in the medical industry, the non-use scenario would

thus have significant economic impacts for these customers as they would have to purchase new diagnostic equipment, train and requalify personnel in the use of new equipment and revalidate their assay menu according to regulatory guidelines. There could also be health impacts on the consumers of contaminated products in such a case where bioMérieux was unable to supply these industries and where no alternative products/suppliers were available.

Although not quantified, SEAC agrees with the applicant that the health related impacts of non-authorisation are likely to be significant.

Unemployment impacts

The working hours of bioMérieux's workers for the production of products of the use applied for have been considered as potentially lost in the context of the non-use scenario. The applicant estimates that in case of a non-granted authorisation 8.6 directly associated jobs would be lost. The applicant uses two different approaches for estimating the associated social cost of unemployment. The first is based on the default welfare cost factor of 2.7 outlined in SEAC's note on the social cost of unemployment and gives a value of €544 548. The second approach, also endorsed by SEAC, applies the methodology proposed by Dubourg (2016)[14]. Using the latter method, the applicant calculates a cost of €309 850 (revised value following SEAC scrutiny) in total, based on lost wages, average unemployment duration, the impact of scarring (i.e. the impact of being made unemployed on future earnings and employment possibilities), cost of searching for a new job, recruitment costs and value of leisure time. Indirect jobs that would be lost as a result of reduced activity in related functions such as logistics, sales, marketing, packaging etc. have not been accounted for. The more conservative value is taken into account by the applicant in the impact assessment.

In the comments on the draft opinion, the applicant explains that it expects the increased demand for its extraction buffers resulting from the COVID-19 crisis to lead to a significant increase in working hours in the coming years. However, since bioMérieux is currently not able to quantify the increase in employment, it considers that job losses are unchanged from the initial assessment in order to be conservative.

[14] Dubourg (2016): https://echa.europa.eu/documents/10162/13555/unemployment_report_en.pdf/e0e5b4c2-66e9-4bb8-b125-29a460720554

Table 8: Socio-economic benefits of continued use

Description of major impacts	Quantification of impacts (over the requested review period)
1. Benefits to the applicant and/or their supply chain	
1.1 Avoided profit loss due to investment and/or production costs related to the adoption of an alternative	Not relevant
1.2 Avoided profit loss due to ceasing the use applied for	€10-225 million
1.3 Avoided relocation or closure cost	Not relevant
1.4 Avoided residual value of capital	Not relevant
1.5 Avoided additional cost for transportation, quality testing, etc.	Not relevant
Sum of benefits to the applicant and/or their supply chain	*€10-225 million*
2. Quantified impacts of the continuation of the SVHC use applied for on other actors	
2.1 Avoided net job loss in the affected industry	€0.3 million
2.2 Foregone spill-over impact on surplus of alternative producers	Not quantified
2.3 Avoided consumer surplus loss (e.g. because of inferior quality, higher price, reduced quantity, etc.)	Not quantified
2.4 Avoided other societal impacts (e.g. avoided CO_2 emissions or securing the production of drugs)	Not quantified
Sum of impacts of continuation of the use applied for	*€0.3 million*
3. Aggregated socio-economic benefits (1+2)	**€10-225 million**

5.3. Combined assessment of impacts

The applicant assesses that the monetised costs of the non-use scenario would be in the range of €100 million to €1.5 billion taking into account lost revenues as well as the costs of unemployment. Taking the impacts in one year alone (2022 is taken to be the reference year), the monetised impact is estimated by the applicant in the range of €100-500 million. As discussed in the previous section, however, it is more appropriate to use profits as a measure of the economic impacts rather than revenues. Assuming a constant profit rate of 10-15 % of revenue as indicated by the applicant in response to SEAC questioning, SEAC estimates that the combined cost of lost profits and unemployment in the non-use scenario would be in the range of €10-225 million for the requested review period and €10-75 million for one year alone.

As a complementary argument to demonstrate that the benefits of continued use exceed the risks, the applicant presents a cost-effectiveness analysis, again considering lost revenue and the costs of unemployment for one year (2022). This cost (€100-500 million) is divided by the expected substance release in one year (2.08 kg) resulting in a cost-effectiveness ratio in the range of around €48-240 million per kg released. Using foregone profits rather than lost revenue (and assuming that profits are 10-15 % of revenue) SEAC finds that the ratio is significantly reduced and is in the range of €5-36 million per kg released. Other economic impacts described qualitatively by the applicant are not considered in the quantitative comparison of impacts.

Table 9: Socio-economic benefits and risks of continued use

Socio-economic benefits of continued use		**Excess risks associated with continued use**	
Benefits	€10-75 million/year	Monetised excess risks to workers directly exposed in the use applied for	Not relevant
Quantified impacts of the continuation of the SVHC use applied for	Not quantified	Monetised excess risks to the general population and indirectly exposed workers	Not relevant
Additional qualitatively assessed impacts	Avoided health related impacts resulting from unavailability of NucliSens® extraction products and NucliSens® easyQ® HIV-1 products	Additional qualitatively assessed risks	Environmental impacts associated with releases of 4-tert-OPnEO of 2.08 kg/year
Summary of socio-economic benefits	**Aggregated socio-economic benefits: €10-75 million/year** **Avoided health related impacts resulting from unavailability of NucliSens® extraction products and NucliSens® easyQ® HIV-1 products**	**Summary of excess risk**	**Environmental impacts associated with releases of 4-tert-OPnEO of 2.08 kg/year**

Table 10: Cost of non-use per kg and year

	Per year
Total cost[1] (€)	€10-75 million
Total emissions[2] (kg)	2.08 kg of 4-tert-OPnEO
Ratio[3] (€/kg)	€5-36 million/kg of 4-tert-OPnEO

Notes:

1. "Total cost" (of non-authorisation) = Benefit of authorisation
2. "Total emissions" (if authorisation is granted) = Estimated emissions to the environment, kg per year, based on Table 6
3. "Ratio" = Total cost/Total emissions

5.4. SEAC's view on Socio-economic analysis

SEAC considers that the applicant's non-use scenario, which assumes that production would cease for both NucliSens® extraction products as well as NucliSens® easyQ® HIV-1 products, is justified. The relocation or subcontracting of production outside the EU does not appear

viable given the significant expertise and high level of know-how that is required. Relocation or subcontracting would require significant financial investment and, due to a loss of know-how, could result in a decrease in product performance. In such a scenario, it is likely that the costs of relocation/subcontracting would exceed the benefits. In the case of NucliSens® easyQ® HIV-1 products, for which a discontinuation is planned by not long after the sunset date (certainly a much shorter period of time than the requested review period), SEAC supports the applicant's view that it would not be technically or economically prudent to consider relocating or subcontracting.

SEAC accepts the applicant's argument that a downgrading of product performance that may arise from non-optimal substitution cannot be considered either, given the high level of requirement in terms of reliability of the extraction process provided to end users.

The main economic impact item considered by the applicant is foregone revenue that would result over a 12 year time frame in the non-use scenario. SEAC assessed that the applicant had initially overestimated the benefits of continued use by basing the economic impacts on revenue losses and assuming an inappropriate revenue growth rate over the 12 year review period. In response to a SEAC request, the applicant subsequently revised downwards its revenue forecasts and provided a profit rate on revenues of 10-15 % based on the 2015-2017 period. A further update of the revenue forecasts has been provided by the applicant in the comments on the draft opinion to take into account the increased demand for its extraction buffers resulting from the COVID-19 crisis. Applying the profit rate provided by the applicant to the estimate of lost revenues provided in the comments on the draft opinion would result in a profit loss estimate in the range of €10-225 million over the requested review period. However, SEAC notes the difficulties inherent in forecasting over long periods, in particular in light of the COVID-19 related uncertainties referred to by the applicant. Both the revenue estimates and the profit rate provided by the applicant could vary over time and some proportion of such a loss could be regained gradually under the non-use scenario as activities/resources are redeployed to areas unaffected by non-authorisation.

Given the applicant's large market share, the high performance demands on the products and the regulatory requirements, SEAC finds it credible that competitors would not be able to take over the applicant's market share in the short or medium term. However, it is not possible to determine when this may happen and hence the precise period for which profit losses should be considered is unclear. SEAC notes that considering only one-year profit losses would still imply economic impacts in the range of around €10-75 million.

The reasons for inclusion of various costs are transparent although exact costs of various items such as relocation or subcontracting, loss of secondary markets and hypothetical costs such as penalties for breaking contractual arrangements were not assessed quantitatively. Nevertheless, the applicant has provided sufficient information to allow SEAC to assess the robustness of the measures and has demonstrated that net economic welfare would be impacted. The applicant also presents details of sunk costs that would be incurred as a result of earlier than planned "end of life" of reagents and associated equipment, however, SEAC does not consider the inclusion of sunk costs when assessing economic impacts.

The qualitative descriptions of the use of the applicant's tests for the diagnosis of various diseases, including COVID-19, demonstrate the value of these products. Between 1 and 10 million extractions were commercialised using the NucliSens® extraction products in 2018 and between 100 thousand and 1 million easyQ® HIV-1 tests were used to monitor the HIV-1 viral load. SEAC, thus, concludes that a large number of patients would be affected in the non-use scenario with potentially very adverse consequences, since delayed diagnosis could increase mortality and treatment costs. SEAC also notes that customers could, potentially, be adversely affected in the food safety, cosmetics and pharmaceuticals and veterinary industries, however,

the number is not estimated by the applicant. Although not quantified, SEAC notes that the premature replacement of workable equipment would present a significant cost to hospitals, laboratories and other end-users.

SEAC considers that the most plausible non-use scenario would result in unemployment of some of the applicant's workers. The applicant provided two estimates of the cost of unemployment, the methodologies for which SEAC approves. The applicant includes only the loss of direct rather than indirect jobs. SEAC agrees that it is prudent to take the most conservative estimate into account when assessing the benefits of continued use. Even using this more conservative approach, SEAC notes that this impact would present a significant welfare cost and can be considered an important benefit of continued use.

While it is not possible to determine the exact cost-effectiveness of the use applied for, SEAC has recalculated the applicant's value based on foregone profits and the cost of unemployment for one year only (2022) and finds that the cost is in the range of €5-36 million per kg released. It should be noted that this number is based on an assumed profit/revenue ratio of 10-15 % and it does not take into account the medical impacts, which would significantly increase the benefits of continued use and, in turn, cost-effectiveness.

5.5. Conclusion on the socio-economic analysis

SEAC has no substantial reservations on the quantitative and qualitative elements of the applicant's assessment of the benefits and the risks to the environment associated with the continued use of the substance. This conclusion is made on the basis of:

- the application for authorisation,
- SEAC's assessment of the benefits of continued use,
- SEAC's assessment of the availability, technical and economic feasibility of alternatives,
- SEAC's assessment of the comments received in the consultation,
- any additional information provided by the applicant,
- RAC's assessment of the risks to the environment.

6. Proposed review period

☐ Normal (7 years)

☒ Long (12 years)

☐ Short (…. years)

☐ Other: _____ years

When recommending the review period SEAC took note of the following considerations:

6.1. RAC's advice

RAC gives no advice on the length of the review period.

6.2. Substitution and socio-economic considerations

The applicant requests a review period of 12 years in order to develop, implement and validate alternatives for the use applied for. When recommending the review period SEAC took note of the following considerations:

- Due to high performance requirements and the regulatory approval process, SEAC finds it credible that it would not be possible for the applicant to substitute within a normal review period.
- SEAC also finds credible the applicant's claim that even if an alternative appears to be technically feasible during initial research, its successful implementation across the entire range of products would require the requested review period.
- SEAC has no reservations on the quantitative and qualitative elements of the applicant's assessment of the benefits and the risks to the environment associated with the continued use of the substance. The applicant's impact assessment was considered by SEAC to provide robust conclusions in this respect.

Although it is difficult to assess the longer term prospects for the development of suitable alternatives, SEAC, having taken into account the above points, considers that a realistic prospect for substitution will not be possible within the timelines of a short or normal review period.

Taking into account these points, SEAC recommends a **12 year** review period.

7. Proposed additional conditions for the authorisation

Were additional conditions[15] proposed for the authorisation?

☐ Yes

☒ No

7.1. Description

RAC

Proposed additional conditions

None.

SEAC

Proposed additional conditions

None.

7.2. Justification

RAC is of view that the applicant has demonstrated that releases to environmental compartments have been prevented or minimised as far as technically and practically possible based on the OCs & RMMs in the ES.

[15] Conditions are to be proposed where RCR is > 1, OCs and RMMs are not appropriate and effective, risk is not adequately controlled, minimisation of emissions is not demonstrated.

8. Proposed monitoring arrangements for the authorisation

Were monitoring arrangements[16] proposed for the authorisation?

☐ Yes

☒ No

8.1. Description

Not applicable.

8.2. Justification

RAC is of view that the applicant has demonstrated that releases to environmental compartments have been prevented or minimised as far as technically and practically possible based on the OCs & RMMs in the ES.

9. Recommendations for the review report

Were recommendations for the review report made?

☒ Yes

☐ No

9.1 Description

RAC recommends that the applicant should continue quarterly / 4 times/year monitoring of 4-tert-OPnEO (parent substance and its main degradation products) in the wastewater prior to release to the local STP using an analytical method capable of adequately characterising the substance in water and at an appropriately low level of detection. The results should be included in any subsequent review report, including details of the sampling point, the analytical method, the concentrations detected and the corresponding environmental release values.

RAC recommends the applicant to further assess in any review report the feasibility to collect the liquid wastes from washing the glassware and put it in practice if the outcome of the feasibility study is favourable.

9.2 Justifications

The quarterly monitoring program, which the applicant already committed to take forward during the review period, should address the current shortcomings of the release estimates (limited number of measurements and discrepancy in the results) and should confirm the effectiveness of the OCs and RMMs in place.

[16] Monitoring arrangements for the authorisation are to be proposed where RCR is < 1, OCs and RMMs are appropriate and effective, risk is adequately controlled, minimisation of emissions is demonstrated – but there are some moderate concerns.

10. Comments on the draft final opinion

Did the applicant provide comments on the draft final opinion?

☒ Yes

☐ No

10.1. Comments of the applicant

Was action taken resulting from the analysis of the comments of the applicant?

☒ Yes

☐ No

☐ Not applicable – the applicant did not comment

10.2. Reasons for introducing the changes and changes made to the opinion

In its draft opinion, SEAC considered that the applicant had not submitted a substitution plan. Even though the applicant covered most of the elements required in a substitution plan in the AoA/SEA report and in the responses to SEAC questions, a description of how the implementation of the substitution plan will be monitored was missing. In its comments on the draft opinion, the applicant provided an overview table with references to the relevant sections in the AoA/SEA report and the responses to SEAC questions indicating where the factors affecting substitution and the list of actions and timetables with milestones are described. In addition, the applicant complemented this overview table with a description of how the implementation of the substitution plan will be monitored. SEAC acknowledges the applicant's description of the monitoring of the implementation of the substitution plan in section 4.4 above and, in light of the applicant's comments, considers that a substitution plan has been submitted.

Furthermore, some of the applicant's activities under Use 1 have been severely impacted as the demand for 4-tert-OPnEO-containing extraction buffers has increased dramatically due to the COVID-19 crisis. Therefore, the applicant has updated the CSR based on a hypothetical maximum tonnage used on-site and regular analytical monitoring of the releases to the environment. Additionally, the applicant has provided updated information relating to the socio-economic impacts of continued use taking into account the increased demand for its extraction buffers. The applicant has also explicitly stated that neither the AoA nor the substitution plan nor the most likely non-use scenario are affected by their COVID-19-related activities. The draft opinion has been therefore updated in the relevant sections based on the applicant's newly submitted information.

In addition, minor editorial changes were made.

10.3. Reasons for not amending the opinion

Not applicable.