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

Industrial use of 4-tert-OPnEO for its "wetting" detergent properties in the production of buffers, reagents and gel supports allowing the dissolution, the dilution and the good spreading of substrates and reagents, necessary to optimize the functioning and the sensitivity of gel electrophoresis in vitro diagnostic test

Submitting applicant

SEBIA

ECHA/RAC/SEAC: AFA-O-0000006699-55-01/D

Date: 11/06/2020

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(s)	**SEBIA** (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) 618-344-0 9002-93-1
Intrinsic property(ies) 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), please specify: Endocrine disrupting properties - environment
Use title	**Use 1: Industrial use of 4-tert-OPnEO for its "wetting" detergent properties in the production of buffers, reagents and gel supports allowing the dissolution, the dilution and the good spreading of substrates and reagents, necessary to optimize the functioning and the sensitivity of gel electrophoresis *in vitro* diagnostic test**
	Other connected uses: Use-2: Industrial use of 4-tert-OPnEO for its detergent properties in the production of electrophoresis gels in view of ensuring the positioning of specific proteins necessary for the interpretation of results of in vitro diagnostic test based on protein separation Use-3: Industrial use of 4-tert-OPnEO for its detergent properties resulting in cellular lysis and protein interactions rupture and required for the production of reagents involved in

	the determination of proteins of interest in gel and capillary electrophoresis IVD tests
	Same uses applied for: not applicable
Use performed by	☒Applicant(s) ☒Downstream User(s) of the applicant(s)
Use ID (ECHA website)	0141-01
Reference number	11-2120809924-49-0001
RAC Rapporteur RAC Co-rapporteur	VAN DER HAAR Rudolf LEINONEN Riitta
SEAC Rapporteur SEAC Co-rapporteur	LEAHY Eimear
ECHA Secretariat	MARQUEZ-CAMACHO Mercedes HENRICHSON Sanna LIOPA Elīna

PROCESS INFORMATION FOR ADOPTION OF THE OPINIONS

Date of submission of the application	11/02/2019
Date of payment, in accordance with Article 8 of Fee Regulation (EC) No 340/2008	27/05/2019
Application has been submitted by the Latest Application Date for the substance and applicant(s) can benefit from the transitional arrangements described in Article 58(1)(c)(ii).	☒Yes ☐No
Public 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/23322/del/200/col/synonymDynamicField_302/type/asc/pre/2/view
Request for additional information in accordance with Article 64(3)	24/05/2019, 01/07/2019, 22/07/2019 and 07/08/2019 Link: https://echa.europa.eu/applications-for-authorisation-previous-consultations/-/substance-rev/23322/del/200/col/synonymDynamicField_302/type/asc/pre/2/view
The trialogue meeting	06/08/2019
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 Comment: none
Agreement of draft opinion in accordance with Article 64(4)(a) and (b) on	RAC: 05/12/2019, agreed by consensus.
	SEAC: 20/09/2019, agreed by consensus.

Date of sending of the draft opinion to applicant	07/02/2020
Date of applicant's decision to comment on the draft opinion, according to Article 64(5)	16/03/2020
Date of receipt of applicant's comments, according to Article 64(5), received	14/04/2020
Adoption of opinion, according to Article 64(5), on	RAC: 11/06/2020, adopted by consensus.
	SEAC: 11/06/2020, 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(s) 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 0.066 kg/year (according to monitoring data) or 4.4 kg/year (according to default release values from ERCs) 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 of the substance in accordance with Annex I of the REACH Regulation.

The following alternatives have been assessed:

- BRIJ® 35 (CAS 9002-92-0)
- DIGITONIN (CAS 11024-24-1)
- TWEEN® 20 (CAS 9005-64-5)
- TWEEN® 80 (CAS 9005-65-6)
- DODECYL-β-D-MALTOPYRANOSIDE (CAS 69227-93-6)
- OCTYLGLUCOSIDE (CAS 29836-26-8)

(See section 4 of the justifications).

SEAC concluded on the analysis of alternatives and the substitution plan that:

- By the Sunset date[1] 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 was 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 €14 million over the requested review period and additional important benefits to society have been assessed qualitatively but have not been monetized. This includes the availability of electrophoresis kits for the diagnosis of chronic diseases (characterised by e.g. enzymatic dysfunction or overproduction) and for rare and difficult to diagnose diseases, such as Waldenström disease or Multiple Myeloma.
- 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[2].

SEAC considered that if an authorisation was refused, the use of the substance could (in the long term):

- be substituted by market actors operating inside the EU, or
- 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[3] at least 133 jobs would be lost.

PROPOSED CONDITIONS AND MONITORING ARRANGEMENTS, AND RECOMMENDATIONS

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

REVIEW PERIOD

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

[1] For AfAs submitted before the LAD
[2] The formulation of this conclusion may be adapted in future versions of this format.
[3] 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(s) in the supply chain	Upstream ☐ [group of] manufacturer[s] ☐ [group of] importer[s] ☐ [group of] only representative[s] ☐ [group of] formulator[s] Downstream ☒ group of downstream users
Indicative number and location of sites covered	2 sites: - Lisses, France (SEBIA); - Paladru, France (REXOR, sub-contractor and downstream user of SEBIA);
Annual tonnage of Annex XIV substance used per site (or total for all sites)	Lisses, France (SEBIA): 100 kg Paladru, France (REXOR): 0.6 kg Total volume: 100.6 kg [4]
Function(s) of the Annex XIV substance	The substance is used for its detergent properties in the production of gel electrophoresis *in vitro* diagnostic (IVD) devices.
Type of products (e.g. articles or mixtures) made with Annex XIV substance and their market sectors	Product: Gel electrophoresis IVD tests kits (HYDRAGEL® product range) Market sector: Analytical laboratories, hospitals
Shortlisted alternatives discussed in the application	Alternative substances considered: • BRIJ® 35 (CAS 9002-92-0) • DIGITONIN (CAS 11024-24-1) • TWEEN® 20 (CAS 9005-64-5) • TWEEN® 80 (CAS 9005-65-6) • DODECYL-β-D-MALTOPYRANOSIDE (CAS 69227-93-6) • OCTYLGLUCOSIDE (CAS 29836-26-8) Alternative technologies considered: none Others: -
Annex XIV substance present in concentrations above 0.1 % in	☒Yes ☐No

[4] According to the applicant these values correspond to the maximum amount of 4-tert-OPnEO expected to be used in 2022.

the products (e.g. articles) made	☐Unclear ☐Not relevant
Releases to environmental compartments	☐Air ☒Water ☐Soil ☐None
The applicant(s) have used the PNEC recommended by RAC	☐Yes ☐No ☒Not relevant
All endpoints listed in Annex XIV were addressed in the assessment	☒Yes ☐No If 'No' – which endpoints are not adressed
Adequate control concluded by applicant for the relevant endpoint(s)	☐Yes ☐No ☒Not Applicable – non-threshold substance
Level of (combined, daily / shift-long) exposure/release used by applicant (s) for risk characterisation	<u>Release</u> Water: Lisses, France (SEBIA) (total of Uses 1, 2 and 3): 1.- Based on monitoring data: - 0.042 kg/year (2017) - 0.066 kg/year (projected for 2022) (measured as the sum of OP, OP1EO and OP2EO) 2.- Based on default release values (ERC 2): - 4.4 kg/year Paladru, France (REXOR) (Use 1) 1. Based on monitoring data: - 6×10^{-6} kg/year (measured as the sum of OP, OP1EO and OP2EO) 2.- Based on default release values (ERC 3): - 1.2×10^{-3} kg/year Air: 0 kg/year (considering the low vapour pressure of the substance , emissions to air are considered negligible) Soil: 0 kg/year (the substance is handled indoor, direct releases to soil are not likely)

Risk characterisation	Environmental compartments: The applicants did not attempt to derive PNECs or RCRs. The CSR describes how the OCs and RMMs in the exposure scenario 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 the Hydragel® assays
Applicant(s) concludes that benefits of continued use outweigh the risks of continued use	☒ Yes ☐No ☐Not Applicable – threshold substance with adequate control
Applicant’s(s’) benefits of continued use	For the review period argued: €1.5 billion
Society’s benefits of continued use	Availability of electrophoresis kits for the diagnosis of chronic diseases (characterised by e.g. enzymatic dysfunction or overproduction) and for rare and difficult to diagnose diseases, such as Waldenström disease or Multiple Myeloma
Monetised health impact on workers	Not relevant
Distributional impacts if authorisation is not granted	Not available
Job loss impacts if authorisation is not granted	€57.9 million

SUMMARY OF RAC AND SEAC CONCLUSIONS[5]

1. Operational Conditions and Risk Management Measures

1.1. Conclusions of RAC

Conclusion for environment

Since all relevant solid waste which had been in contact with 4-tert-OPnEO is collected and disposed of as waste for incineration and the relevant wastewater is collected for subsequent treatment on-site (evapo-concentrator) or for incineration off-site, no relevant shortcomings to the operational conditions (OCs) and risk management measures (RMMs) have been identified.

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

☒Yes ☐No

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

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

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

☐Yes ☒No

[5] The numbering of the sections below corresponds to the numbers of the relevant sections in the Justifications.

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

☐Yes ☒No

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

☒Yes ☐No

3. Risk Characterisation

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[6] and as concluded by RAC at its 50th meeting.

Based on the OCs & RMMs in the exposure scenario, in particular the collection and adequate treatment of solid and liquid wastes, 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 0.066 kg/year (according to monitoring data) or 4.4 kg/year (according to default release values from ERCs) of the substance to the environment.

4. Analysis of alternatives and substitution plan[7]

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

100.6 kg

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

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

7 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*".

Has the applicant submitted a substitution plan?

☒Yes ☐No

Conclusions of SEAC

In SEAC's view, the applicant's analysis of alternatives was not comprehensive and, therefore, clarifications were required on several issues. Nevertheless, SEAC is of the opinion that the application, in conjunction with the additional information that was provided, provides a sufficient level of detail to conclude on the current technical and economic feasibility of the alternatives and the derived review period requested by the applicant. The comment received during the public consultation presented alternatives that would require the same overall substitution steps as those shortlisted by the applicant. The applicant listed and described each phase in the substitution initiative and set specific timelines for completion. In response to SEAC's request, the applicant elaborated on the key steps of the substitution process.

SEAC concurs with the applicant that there is currently no technically feasible alternative. SEAC considers that the substitution timelines proposed by the applicant are reasonable considering the additional resources required for the substitution process. The substitution plan was credible and consistent with the analysis of alternatives and the socio-economic analysis.

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

☐Yes ☒No

Does SEAC make any recommendations to the applicant(s) 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 feasibility and economic viability of alternatives,
- any additional information provided by the applicant or its downstream users,
- 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

Monitoring arrangements ☐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
SP	☐Yes	☒No
SEA	☐Yes	☒No

10. Applicant(s) comments on the draft opinion

Has the applicant commented the draft opinion?

☒Yes ☐No

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

☒Yes ☐No

JUSTIFICATIONS

0. Short description of use

SEBIA applied for the industrial use of 4-tert-OPnEO for its "wetting" properties allowing the dissolution, the dilution and the good spreading of substrates and reagents, necessary to optimize the sensitivity of gel electrophoresis in vitro diagnostic tests (IVD) (Use 1).

Use 1 is performed at two sites in France, the site of Lisses (SEBIA) and the site of Paladru (REXOR). The site of Lisses uses a maximum of 100 kg (expected for 2022) of 4-tert-OPnEO as Triton™ X-100 and Triton™ X-405 in the production of gel electrophoresis IVD kits and reagents. The site of Paladru uses 0.6 kg/year of 4-tert-OPnEO as Triton™ X-100 in the manufacture of gel electrophoresis supports. These supports manufactured at Paladru are subsequently used at the site of Lisses for the manufacture of gels for the gel electrophoresis IVD kits.

SEBIA has applied for two additional uses (Use 2 and Use 3) which are interrelated with Use 1. Use 2 covers the use of 4-tert-OPnEO at the site of Lisses (SEBIA) and Rome (INTERLAB) in the manufacture of gels for gel electrophoresis IVD tests, while Use 3 covers the use of 4-tert-OPnEO at the site of Lisses (SEBIA) for the formulation of washing and haemolysis solutions for gel and capillary electrophoresis IVD kits. The relation between the different uses, exposure scenarios and productions sites is illustrated in Figure 1.

These electrophoresis IVD kits are used in laboratories and clinical hospitals to diagnose various pathologies including blood diseases, haemoglobin abnormalities, cancers or infectious diseases.

Although the applicant described the exposure scenario of the use of the IVD kits 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 of Authorisation duties 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 and consequently no reference to the end-user exposure scenario is made in this opinion document. RAC has not evaluated if the conditions for the SR&D exemption have been met.

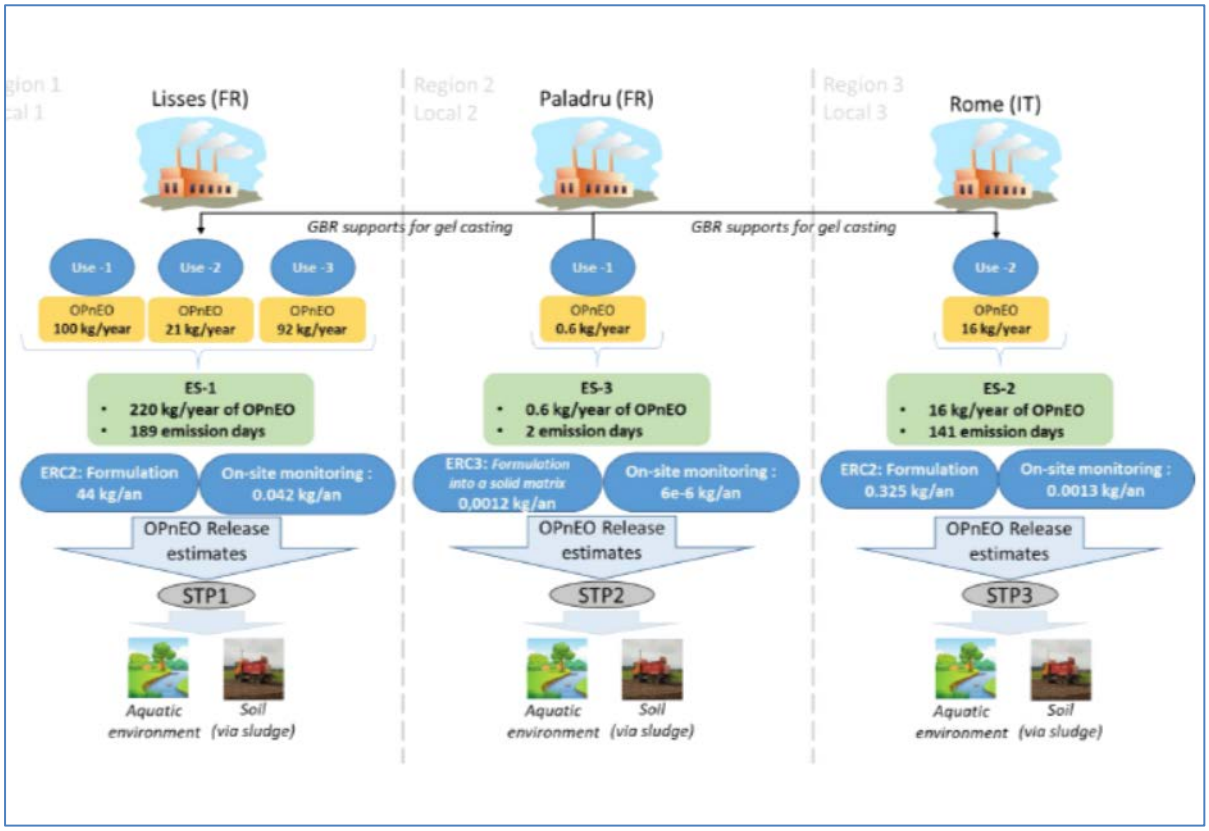

Figure 1: Overview of the relationship between Uses, ESs and production sites

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

Lisses, France (SEBIA)

1. *Supply and storage*

Solutions of Triton X-100 and Triton X-405 are provided in plastic bottles (of 10 L and 1 L respectively) and stored in a specific closed storage room for hazardous products. All liquid products are stored on retention tanks or in watertight tanks.

2. *Quality control*

Quality control is performed in a laboratory dedicated to the validation of all SEBIA products. Samples of Triton™ X-100 and X-405 are sampled in the room dedicated to the weighing (see step 3 below) in Falcon® tubes, hermetically closed and brought to the laboratory. A portion of the sample is kept in the sample bank. Reagents produced in high volumes, are controlled in this laboratory before their packaging.

3. *Weighing*

Triton™ X-100 and X-405 solutions are weighed under a laminar flow cabinet in a semi-enclosed and ventilated area. After weighing, the glassware is rinsed once and the washing water is added to the in-process solution. The glassware is sent to the laundry room for the final washing step.

4. *Mixture/formulation*

The applicant describes two different formulation processes:

- Formulation of reagents for gel and strip production

  This step consists of the formulation of solutions of Triton™ X-100 and X-405 to prepare

buffers for both gel and strip productions :

a) For gel buffers, the operation is performed in the semi-enclosed and ventilated weighing room using semi-automatic mixers and barrels or tanks (≤ 200 L)

b) For strip buffers, the operation is performed in the semi-enclosed and ventilated room dedicated to reagent production using semi-automatic reagent mixing tanks (for low volume = 200 L to 500 L).

The buffer mixtures are hermetically closed during this step.

- Formulation of reagents for IVD kits

This step consists of the formulation of solutions of Triton™ X-100 to prepare reagents for IVD kits:

a) For reagents packaged in high volume bottles (750 mL, 250 mL and 100 mL), the operation is performed in a semi-enclosed and ventilated room dedicated to reagent production using semi-automatic reagent mixing tanks (for high volume = 1 500L to 5 000 L) The equipment is directly connected by pipes to the automatic packaging machine placed in a dedicated room.

b) For reagents packaged in low volume vials (few tens µL to mL), the operation is performed in a semi enclosed and ventilated room dedicated to reagent productions using semi-automatic reagent mixing tanks (for low volume = 200 L to 500 L) or directly in the semi-enclosed and ventilated weighing room using semi-automatic mixers and barrels or tanks (for low volume < 200 L). For this process, movements between mixture rooms and packaging rooms (mainly manual) are performed with trolley. The mixtures are hermetically closed during this step.

5. Production of final products

- Gel production by casting

The gel is manufactured from the reagents formulated in the previous steps and an intermediate plastic material coated (GBR[8] support) produced by a subcontractor at Paladru site (ES3). This operation is carried out in an automated casting machine in a dedicated clean room under controlled atmosphere. Finally, gels are packaged individually and then stocked in an identified container until their final conditioning.

- Gel production by moulding

This operation is performed for specific SEBIA products and consists of the manufacturing of gel from the reagents formulated in the previous step and an intermediate plastic material coated (GBR support) produced by a subcontractor at Paladru site (ES3). This operation is carried out by manual moulding, demoulding and control performed by trained staff. Finally, gels are packaged individually and then stocked in an identified container until their final conditioning.

- Buffered strips production

A minor part of the polyvinyl alcohol (PVA) sponges needed for this step is first washed in a dedicated washer. Then, PVA sponges are shaped and cut using a semi-automated machine to produce strips. Finally, strips are packaged individually and then stocked in an identified container until their final conditioning.

[8] GBR support is composed of a plastic film recovered with a solution containing Triton X-100 (0.0026 % w/w) which is coated and dried to produce a technical support needed to get a good gel casting.

6. *Packaging*

Once produced, coated, moulded gels and strips are immediately packaged with their respective buffers with automated and dedicated equipment. High-volume reagents (750 mL, 250 mL and 100 mL) are directly transferred from mixing vessels to the automated packaging machine by pipes. For some low-volume reagents (few tens µL to mL), the packaging step is performed manually by trained staff using automated pipettes in dedicated and ventilated rooms. More generally, low-volume reagents are packaged using semi-automated or automated equipment in dedicated and ventilated rooms. Finally, gels, strips, and reagents are conditioned in cardboard IVD packs before their distribution.

Paladru, France (REXOR)

The production of the gel electrophoresis supports (GBR) takes place at Paladru, France. The GBR support is composed of a plastic film coated with a solution containing Triton X-100 (0.0026 %) which is used in the manufacturing of gel by casting and moulding at SEBIA site in Lisses (ES-1).

1. *Supply and storage*

4-tert-OPnEO is supplied by Sebia as a 5 % solution of Triton™ X-100 in 5-L sealed plastic bottles and stored in a locker room in the production area.

2. *Weighing*

Volumes of Triton™ X-100 solutions (5 %) provided by SEBIA are measured in a ventilated area. The glassware is rinsed and the washing water is collected in dedicated containers for incineration. The glassware is then transferred to the laundry rooms for the final washing.

3. *Mixture and formulation*

Volumes of Triton™ X-100 solutions (5 %) are mixed in a heated (60 L) autopreparer and transferred to the the coating line via a peristaltic pump. These operations are performed in a semi-enclosed production equipment in an open area.

4. *Production of intermediate products*

The coating and drying of the plastic films is carried out in an automated production line equipped with air extraction and filtering system.

5. *Intermediate packaging*

Once produced and dried, the gel supports (GBR) are cut into a narrower scroll with an automated equipment, packed and transported by a certified company to the SEBIA site at Lisses.

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

According to the applicant, 4-tert-OPnEO is used for its detergent properties to ensure the dissolution, solubilisation and good spreading of substrates and reagents in gel electrophoresis in vitro diagnostic tests.

The main functional properties include:

- Optimization of the molecules' migration by solubilization and stabilisation of proteins in order to improve test sensitivity and reproducibility,
- Medium wettability conditions required for support-dependant reactions and optimization of the test sensitivity,
- Continuity between electrophoresis elements and solutions in view of increasing test sensitivity and reproducibility.

0.3. Type(s) of product(s) made with Annex XIV substance and market sector(s) likely to be affected by the authorisation

Use 1 concerns the use of 4-tert-OPnEO in gel electrophoresis in vitro diagnostic tests. SEBIA products affected by Use 1 are the HYDRAGEL® product range. HYDRAGEL ® is a product range of gel electrophoresis assays for the identification and the quantification of proteins which are specific markers of certain pathologies. HYDRAGEL ® assays are used by professionals in hospitals or laboratories to diagnose various pathologies, including blood diseases, haemoglobin abnormalities, cancers or infectious diseases.

1. Operational Conditions and Risk Management Measures

1.1. Environment

The applicant presented two contributing exposure scenarios, one for each of the sites:

- ES-1: production of buffers and reagents for *in vitro* electrophoresis assays at Lisses, France (SEBIA)(ERC-2: Formulation into mixture)
- ES-3: production of gel electrophoresis supports at Paladru, France (REXOR, a sub-contractor) (ERC-3: Formulation into a solid matrix)

A summary of the OCs and RMMs in the environmental contributing scenarios is provided in Table 1. The detailed conditions of use are available from sections 9.2 and 9.4 of the CSR.

Table 1: Operational conditions

	ES-1 (covering Uses 1, 2 and 3, Lisses)	**ES-3 (Use-1, Paladru)**
Volume used per year	Total 130 kg (2017) Total 220 kg (2022)* - 100 kg (Use 1, 2022) - 21 kg (Use 2, 2022) - 93 kg (Use 3, 2022)	0.6 kg (2017) 0.6 kg (2022)
Number of days of release per year	189	2
Concentration of 4-tert-OPnEO	Triton™ X-100 > 99.7 % at the beginning of the process; Triton™ X-405: 70 % at the beginning of the process; 0.01-5 % in end products (IVD kits)	Triton™ X-100: around 5 % at the beginning of the process
Daily release of 4-tert-OPnEO	0.35 g/day (based on monitoring**) (total of OP, OP1EO and OP2EO) 23.3 g/day (ERC2)	0.003 g/day (based on monitoring)(total of 4-tert-OP, OP1EO and OP2EO) 0.6 g/day (ERC3)

* The applicant has used a rounded figure of 220 kg for the assessment

** Monitoring performed on site was used to estimate the release factor based on the tonnage in use in 2017. The same release factor was applied to the tonnage in use foreseen for 2022 to extrapolate the corresponding releases.

According to the applicant the following RMMs are implemented:

Technical and organisational conditions and measures

- The production site of Lisses (ES-1) operates management systems which comply with the requirements of ISO 14001and ISO 13485[9].
- The production site of Paladru (ES-3) operates a management system which complies with the requirements of the ISO 14001, ISO 9001and OHSAS 18001.
- At both sites , Lisses (ES-1) and Paladru (ES-3):
    - Training of workers, operational procedures for manufacturing and collect/disposal of wastes, safety rules and displays in the work rooms are implemented.
    - In case of accidental spills of 4-tert-OPnEO-containing solutions, intervention kits containing absorbent products are used and soiled materials are placed in a disposable container for incineration.

Waste management

ES-1, Lisses

- Low volumes of 4-tert-OPnEO-containing solutions in equipment and all solid wastes (e.g. used filters of laminar flow cabinet, single-use equipment, soiled vials and empty containers) are collected in dedicated containers, hermetically closed, properly identified as dangerous wastes and stored in a dedicated area before handed over to a certified company for incineration.
- Washing waters of equipment (e.g. mixers, mixing tanks, moulding equipment, automated packaging equipment) are collected by reels and manholes present in production rooms and linked to two external underground retention reservoirs.
- Waste water in retention reservoirs are treated on-site by an evapo-concentrator (boiling at 40 ºC at low pressure). The distillate is released to the collective sewage network to be treated by the local Sewage Treatment Plant (STP).
- Resulting evapo-concentrate as well as some particular liquid or semi-solid wastes (gel) not suitable to be treated in the evapo-concentrator are treated with Osmofilms in the external area and then disposed of by a certified provider company via incineration.
- The incineration of waste (liquid and solid) containing 4-tert-OPnEO is performed by a certified waste operator, traceable through regulatory documents and recorded in an internal regulatory database during at least five years.
- Waste water resulting from the washing of glassware performed during different process steps (weighing, mixture and formulation (see 2.2. Discussion on OCs and RMMs)) is not collected for treatment and therefore identified as potential releases of 4-tert-OPnEO.

ES-3, Paladru

- Solid 4-tert-OPnEO-containing wastes (empty containers, single-used equipment) and liquid 4-tert-OPnEO-containing wastes from process effluents (dead-volumes of solutions and washing waters of equipment) are collected in appropriate containers, hermetically closed, properly identified as special industrial wastes and disposed of by a certified company via incineration.
- Waste waters resulting from rinsing of glassware is collected in dedicated containers for incineration. According to the applicant glassware is rinsed at least two times (the

[9] ISO 13485:2016: *Medical devices – Quality management systems – Requirements for regulatory purposes*

second rinsing step has been introduced after the application was already submitted) and the resulting waste water is collected for incineration.
- 4-tert-OPnEO-contaminated GBR scraps are collected and sold to an external company and then revaluated.
- The incineration of waste (liquid and solid) containing 4-tert-OPnEO is performed by a certified waste operator and traceable through regulatory documents.

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

Since all solid waste which had been in contact with 4-tert-OPnEO, is collected and disposed of as waste for incineration (with the exception of contaminated GBR manufacturing scrap) and the relevant wastewater is collected for subsequent treatment on-site (evapo-concentration) or for incineration off-site, no relevant shortcomings to the OCs and RMMs have been identified.

The only potential emission of 4-tert-OPnEO at the site of Lisses results from the releases to the collective sewage network of: (i) the distillate generated in the evapo-concentrator after treatment of the cleaning waters of the equipment, and (ii) the waste waters resulting from the washing of the glassware used in the weighing and formulation steps of the process. According to the applicant, the release 4-tert-OPnEO resulting from the last washing step of the glassware at the Lisses site is potentially negligible, since the glassware is already rinsed once during the weighing step, and the resulting solution is added to the formulation. In spite of that, the applicant has started an analysis of the process in order to implement a second rinse of the glassware and collect the rinse water before sending the glassware to the laundry room for the final washing. In addition to that, the applicant is currently considering the technical feasibility to connect the washing machine present in the laundry room to the external underground retention reservoirs and to treat the resulting water by evapo-concentration.

According to the applicant, no releases of 4-tert-OPnEO can be expected from the process at the Paladru site. The applicant has introduced a second rinse step of the contaminated glassware (after submission of the AfA) and the washing water of both rinsing steps are now collected in dedicated containers for incineration. According to the applicant, the collection of washing water of glassware resulting from the weighing steps can be considered fully achieved in Paladru and no release to water is expected.

The applicant is commited to implement a yearly monitoring system at both sites (Paladru and Lisses) to verify the efficiency of the RMMs implemented.

1.3. Conclusions on OCs and RMMs

Overall conclusion

Are the operational conditions and risk management measures appropriate[10] and effective[11] in limiting the risk for workers, consumers, humans via environment and / or environment?

Workers ☐Yes ☐No ☒Not relevant

[10] 'Appropriateness' – relates to the following of the principles of the hierarchy of controls in application of RMMs and compliance with the relevant legislation.
[11] '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.

Consumers	☐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.

2. Exposure assessment

2.1. Environmental emissions

Air

According to the applicant, releases to air are negligible taking into account the activities performed and the low vapour pressure of the substance.

Soil

No direct releases to soil are expected based on the use of the substance.

Water

The applicant has followed two different approaches to estimate the releases rates to water:

1) Monitoring data:

The applicant has monitored the concentration of octylphenols in the waste waters at the point of discharge to the municipal sewage network for each site in 2018-19.

Alkylphenol (4-tert-OP) and alkylphenol ethoxylates (OP1EO and OP2EO) have been measured according to ISO18857:2 by certified laboratories. The release rate is estimated based on the volumes in use in 2017-2018 and assumed to remain constant in 2022.

The measurements of the environmental concentration of 4-tert-OPnEO and the calculated release rate are presented in Table 2 and 3 below:

Table 2: Measurements at the site of Lisses (Uses 1,2 and 3)

Date	November 2018	December 2018	January 2019	Max measured
	µg/L	µg/L	µg/L	µg/L
4-tert-OP	0.9	0.92	1.4	1.4
OP1EO	0.16	1	1.8	1.8
OP2EO	0.72	0.49	6.1	6.1
Total alkylphenols	1.78	2.41	9.3	9.3
Tonnage 2017/2018: 128.4 kg/year; number of emission days 189, maximum wastewater discharge 23760 L/day				
Release rate: 0.03 %				

Table 3: Measurements at the site of Paladru (Use 1)

Date	October 2018*
	µg/L
4-tert-OP	0.2
OP1EO	0.58

OP2EO	0.19
Total alkylphenols*	0.97
Tonnage 2017/2018: 0.6 kg/year; number of emission days 2; maximum wastewater discharge 3 200 L/day	
Release rate: 0.001 %	

*Measurements were performed before the collection for incineration of waste waters from second rinse of glassware was implemented.

The LOQs of the analytical method is 0.05 µg/L for OP1EO/OP2EO and OP.

Releases are estimated from the sum of the three measured degradation components (4-tert-OP, OP1EO and OP2EO) without correcting for the rest of the degrading 4-OP9.5EO (Triton X-100) and 4-OP35EO (Triton X-405). At the Lisses site, where three set of measurements are available, the maximum value of 9.3 µg/L corresponding to the January 2019 monitoring data are used for the calculation of the release rate.

2) Default release rate (ERC):

The following release rates are estimated as default worst cases based on the corresponding ERCs: Lisses site: 2 % (ERC 2); Paladru site: 0.03 % (ERC 3).

Based on these two approaches, the applicant has estimated the following releases to water.

Table 4: Estimated emissions of 4-tert-OPnEO to water

	Volume (kg/year)	Release rate		Estimated releases	
		Monitoring	ERC	Monitoring	ERC
Lisses site (ES-1)	Use 1: 100 kg/year Use 2: 21 Kg/year Use 3:92 kg/year Total: 220 kg*	0.03 %	2 %	66 g/year (total Use-1, Use-2, Use-3)	4 400 g/year (total Use-1, Use-2, Use-3)
Paladru site (ES-3)	Use 1: 0.6 kg/year	0.001 %	0.2 %	6×10^{-3}g/year	1.2 g/year

*The applicant has used a rounded figure of 220 kg for the assessment

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

There are residual releases to the local municipal STP from the washing of the glassware at the sites of Lisses and Paladru. At the site of Lisses also the distillate from the evapo-concentrator is released to the collective sewage network to be treated by the local municipal STP.

RAC notes that the release estimate at the site of Lisses has been done for the total volume of 4-tert-OPnEO corresponding to Uses 1, 2 and 3 thus overestimating the release from Use 1. Use 1 covers approximately half of the total volume of use. The applicant acknowledged that the actual monitoring method may lead to uncertainties about the real concentrations of the Triton X-100 and X-405 releases on sites (complex mixture with an average of 9 and 35 ethoxylate units respectively) since the standard method (ISO18857:2) is limited to the detection of alkylphenols ethoxylates up to two ethoxylate units. Besides this, the number of measurements is limited (three measurement data set for Lisses and only one for Paladru) introducing additional uncertainty in the assessment.

In order to overcome the uncertainties, the applicant has performed a release estimate based on the default release rates built in the ERCs. RAC acknowledges the use of an ERC-based assessment as a default worst case estimate. It is to be noted that the RMMs and OCs implemented by the applicant (collection of all relevant solid and liquid wastes for treatment on site (evapo-concentration) or incineration off-site) may lead to a significant reduction of releases compared to those estimated by ERCs.

The applicant informed that yearly monitoring of releases to water will be implemented during the review period at the site of Lisses and Paladru. Furthermore, according to information provided by the applicant, a new and more accurate analytical method is expected to be used, once this new method becomes available. The new analytical method will allow the measurement of all related ethoxylated compounds as OP, which will decrease the uncertainties related to the present methodology limited to the detection of alkylphenols ethoxylates up to two ethoxylate units. These measurement data may be included in a possible review report in order to demonstrate the effectiveness of the OCs and RMMs in place.

As a result of the relatively low vapour pressure of 4-tert-OPnEO (1 Pa at 20 ºC), the type of productions process (laboratory conditions) and the RMMs and OCs in place, RAC concludes 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 that release estimates provided by the applicant are appropriate.

RAC notes that some uncertainties remain related to the low number of measurements and the analytical method available to detect alkylphenols ethoxylates. RAC considers that the actions proposed by the applicant related to the implementation of monitoring of releases to water at the Lisses and Paladru site according to adequate analytical methods (as soon as they become available) are appropriate to address the uncertainties identified.

3. Risk characterisation

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.

Based on the OCs & RMMs in the exposure scenario, the total amount of 4-tert-OPnEO used per year, the collection for treatment on-site or incineration of all relevant solid and liquid wastes, 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).

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 or other benchmark values such as EQSs are available for comparison.

The use applied for may result in emissions of 0.066 kg/year (according to monitoring data) or 4.4 kg/year (according to default release values from ERCs) of the substance to the environment.

4. Analysis of Alternatives and substitution plan[12]

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

100.6 kg

4.1. Summary of the Analysis of Alternatives by the applicant(s) and of the comments received during the public consultation and other information available

Based on a literature review, the applicant has undertaken an initial selection of non-ionic detergents. This class of detergents is expected not to negatively affect the target protein structures involved in the test. The selection of short-listed alternatives was made based on physico-chemical factors critical to ensure proper solubilisation and distribution of proteins along the electrophoresis gel.

The applicant selected alternative detergents with a hydrophilic-lipophilic balance (HLB, the proportion between the weight percentages of hydrophilic head and the lipophilic tail in a surfactant molecule) and a critical micelle concentration (CMC, defined as the concentration of detergents above which micelles are spontaneously formed) as close as possible to those of Triton X-100. The applicant assumed that these alternative detergents could present similar solubilisation and separation properties to Triton X-100. Based on a question from SEAC, the applicant clarified that the only criterium for initially selecting Triton X-100 was its non-ionic property, which is indispensable to avoid side-reactions that may mislead the results of the IVD kits. Triton X-100 gave good results in protein positioning, as well as good repeatability/reproducibility of results.

One alternative was discarded due to its potential SVHC properties, arriving at a shortlist of the following six potential detergents:

- BRIJ® 35 (CAS 9002-92-0)
- DIGITONIN (CAS 11024-24-1)
- TWEEN® 20 (CAS 9005-64-5)
- TWEEN® 80 (CAS 9005-65-6)
- DODECYL-β-D-MALTOPYRANOSIDE (CAS 69227-93-6)
- OCTYLGLUCOSIDE (CAS 29836-26-8)

In addition to the functional properties outlined in Section 1 of this opinion, the applicant has also established analytical performance specifications to ensure that any alternatives are compatible with the analysis instruments provided by the applicant. The applicant states that the six shortlisted alternatives will undergo a series of testing to establish a first functional performance list in order to then identify the most promising alternative.

The applicant has not yet started the feasibility testing of the shortlisted alternatives and states that this is due to a lack of internal resources, with the recruitment of additional staff currently

[12] 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*".

underway.

The applicant considers Tween® 20 a promising alternative as it has already used this to replace Triton X-100 in detergent solutions used in the washing of certain electrophoretic components. However, the applicant states that this recent substitution to Tween® 20 was easily implemented as the only function required was the washing property, which is essentially common to all detergents. Therefore, the applicant states that, as of yet, it cannot say whether Tween® 20 will be the most feasible alternative for the use applied.

The applicant presents the steps required to substitute 4-tert-OPnEO. The specific steps, including technical feasibility at R&D scale, optimisation of industrial scale conditions and industrialisation, regulatory registration and commercial deployment, are discussed in more detail below.

At European level, any in vitro diagnostic medical device used or placed on the market must have a CE-marking according to Regulation No. 2017/745 of 5 April 2017 on medical devices. A change of detergent means that conformity will need to be reassessed and that a new regulatory registration will likely be required. While the regulation of IVD medical devices varies in different markets, regulatory registrations will be needed in all markets where the products are marketed. The applicant states that the time required for the regulatory procedure can vary significantly from one market to another. On average, SEBIA estimates that approximately two years and two months is required to register a single file in all of SEBIA's sales countries. Considering the steps that can be undertaken in parallel and the recruitment of additional staff for the steps requiring extra resources, the applicant concludes that a minimum of 12 years would be needed to substitute.

The cost of recruiting additional staff is estimated to be €9.3 million (NPV in 2018, 4 % discount rate), based on the average annual gross wage of technicians and engineers. The applicant expects the raw material cost of the identified alternatives to be approximately the same as the currently used substances (Triton X100).

One comment received in the public consultation identified five additional alternatives for the applicant’s use of 4-tert-OPnEO:

- ECOSURF EH-9
- ECOSURF EH-9 (90 %)
- ECOSURF SA-9
- TERGITOL TMN-100X (90 %)
- TERGITOL 15-S-9 (the closest matching replacement).

The comment also noted that three other alternatives had been identified in other recent applications for the use of 4-tert-OPnEO:

- TERGITOL™ TMN-10 / TERGITOL™ TMN-6 70 %/30 % mixture
- KOLLIPHOR P-188 (described in AfA 0143-02)
- Tween 20 mixed with ether (described in AfA 0143-03)

A trialogue was held during which the applicant responded to this comment by stating that they were not aware of all these alternatives when preparing the application for authorisation but that they would consider them as part of the substitution process. The applicant highlighted that the toxicity of these alternatives need to be assessed as the applicant is seeking a long-term alternative and would like to avoid any regrettable substitution. However, the applicant noted that, regardless of the alternative, the steps and recruitment costs required to substitute would be the same as those described in the application for authorisation.

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

Not applicable as no technically and economically feasible alternatives are available before the Sunset Date.

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

In SEAC's view, the applicant's assessment is sufficient to conclude on the availability and suitability of alternatives. SEAC considers the applicant's focus on non-ionic alternatives justified to avoid the target protein structures involved in the test being impacted, since this could mislead the IVD test results. However, SEAC notes that the applicant's analysis of alternatives contained inconsistencies and was not comprehensive andenough; that SEAC's evaluation of the analysis required clarifications on several issues, including the applicant's identification of alternatives and the steps required to substitute. Furthermore,While the comment received in the public consultation indicates to SEAC that the applicant's search for alternatives may not have been sufficiently thorough., Nevertheless, SEAC finds it credible that the overall steps required to substitute would be the same for all alternatives, considering the performance and regulatory requirements for medical devices.

In SEAC's opinion, the applicant convincingly demonstrates that technically feasible alternatives will not become available to the applicant before the sunset date because of the substitution steps that are required, such as validation to ensure successful performance of the alternative and regulatory registrations for the required CE-marking. SEAC accepts the applicant's estimation that the time required to register a single file in all of SEBIA's sales countries is approximately two years and two months.

The applicant believes that substitution should be feasible over the requested 12 year review period but notes that technical feasibility can only be confirmed after all the tests have been completed. In the application, the time required for each of the substitution steps was outlined in detail on a per kit-basis. However, SEAC takes note of the applicant's capacity to work on a number of kits in parallel and, thus, questioned the time frames required for carrying out such feasibility tests and implementing an alternative.

From the appplicant's response, SEAC understands that the substitution phase could, in theory, be reduced to 7 years if additional staff was hired. In response to further SEAC questioning,

the applicant provided an estimate of the extra cost that would be incurred as a result of substituting over a 7 rather than 12 year period. SEAC is satisfied that the estimation of these costs is appropriate. According to the applicant, the recruitment cost under a 7 year review period would be €10 million, while it would be €9.3 million under a 12 year review period (NPV in 2018).

As the information provided focuses only on recruitment costs, SEAC notes that these costs can be considered a minimum level and that additional costs are likely to be incurred. The applicant does not provide an exact estimate of such costs but explains that one associated cost would be an investment in facilities to house the extra staff, which, according to the applicant, would amount to several tens of millions of euros. While a major investment would also be required over the requested review period, the applicant states that it would not be as extensive as that required over 7 years. The applicant estimates that a fit for purpose building would take approximately two years to build and, as a result, considers that an alternative would not be operational in 7 years. Since these additional costs are rather speculative and not quantified, SEAC will only consider the recruitment costsdoes not consider them in its evaluation.

SEAC considers that the substitution timelines and associated recruitment costs proposed by the applicant are reasonable.

4.4. Substitution activities / plan

Has the applicant submitted a substitution plan?

☒Yes ☐No

The applicant states that it will pursue the substitution programme described in the application and summarised in Figure 1, if an authorisation is granted. The applicant has confirmed that its intention is to substitute within the review period applied for. The applicant has also provided a credible plan for how the progress of substitution will be monitored.

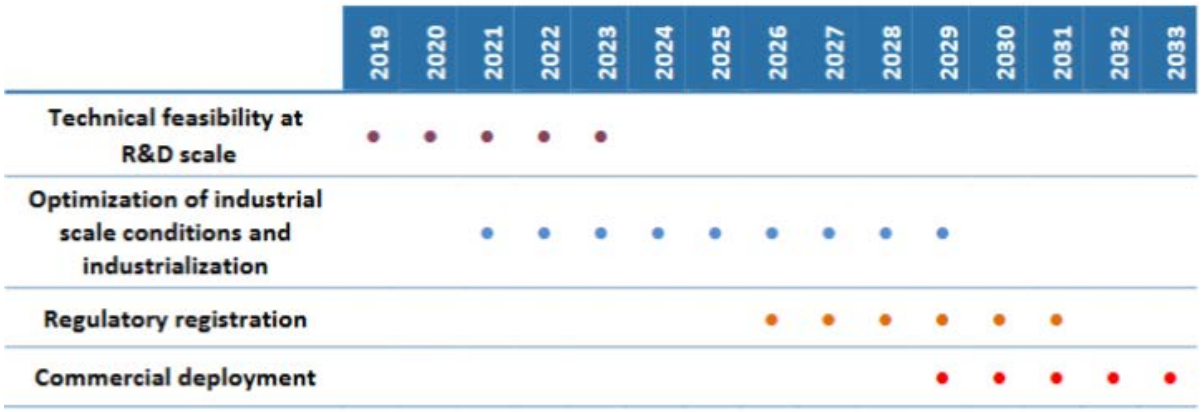

Figure 1. Substitution timeline for the HYDRAGEL® products associated with the use applied for

As explained in section 4.3, SEAC notes that the applicant could possibly develop a suitable alternative ahead of the requested review period of 12 years, but this is only if the alternative will be found technically feasible and extra resources would be allocated to the substitution process. Yet SEAC recognises that the overall costs related to the envisaged substitution set practical limitations on reasonable timelines and that a push for faster substitution would

increase the costs related to R&D.

4.5. Conclusions on the analysis of alternatives and the substitution plan

In SEAC's view, the applicant's analysis of alternatives was not comprehensive and, therefore, clarifications were required on several issues. Nevertheless, SEAC is of the opinion that the application, in conjunction with the additional information that was provided, provides a sufficient level of detail to conclude on the current technical and economic feasibility of the alternatives and the derived review period requested by the applicant. The comment received during the public consultation presented alternatives that would require the same overall substitution steps as those shortlisted by the applicant. The applicant listed and described each phase in the substitution initiative and set specific timelines for completion. In response to SEAC's request, the applicant elaborated on the key steps of the substitution process.

SEAC concurs with the applicant that there is currently no technically feasible alternative. SEAC considers that the substitution timelines proposed by the applicant are reasonable considering the additional resources required for the substitution process. The substitution plan was 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

As outlined in section 3.1, solid waste and wastewater is collected for incineration and only residual release should occur from subsequent rinsing steps. According to RAC, the uses applied for (including releases from use 1, use 2 and use 3 at the Lisses site) may result in releases of up to 66 g/year (according to monitoring data) or 4.4 kg/year (according to default release values from ERCs) of the substance to the environment. For the socio-economic analysis, the applicant has only considered the share of releases assumed to be associated with the use applied for, which it estimates would be 30 grams per year (based on monitoring data). For the purpose of the socio-economic analysis, SEAC will use a range of releases of 30 grams to 4.4 kg per year.

In order to put these releases into context, the applicant has also provided information about the environment in which these releases occur. In relation to SEBIA's sites in Lisses, the applicant explains that the quantities and contamination levels of alkylphenols (nonylphenols, octylpheonls) and their ethoxylates have been frequently measured in the Seine-Normandie basin. These studies show pollution mainly related to PAHs and metals releases. While alkylphenols are part of the pollution, the applicant states that, in comparison with other substances, they have been measured in amounts considered insignificant. Surface water distributions are dominated by nonylphenol (200 ± 80 ng/L), while the concentration of octylphenol and its ethoxyates vary from below the limit of detection (< 1 ng/L) to 10 ng/L and hence do not exceed the annual average environmental quality standards under Directive

2008/105/EC (300 ng/L for nonylphenol and 100 ng/L for octylphenol). The applicant argues that its releases are currently close to zero and will have no environmental impact.

In relation to REXOR's site in Paladru, the Rhône-Méditerranée catchment area shows a pollution which, according to the applicant, is mainly related to industrial hydrocarbon releases. While octylphenol is part of this pollution, the applicant again states that in comparison with other substances, it was measured in amounts considered insignificant. Measurements in the lower Rhône have shown an average annual flow of nonylphenols and para-tert-octylphenols of 197.1 kg per year and 12.6 kg per year, respectively. Sediment samples taken at various stations in the Isère, Drôme and Rhône found that nonylphenols were measured at 7 % of selected sites and that 4-tert-octylphenol was measured at 5 % of selected sites. Contamination measurements have not shown traces of octylphenols at stations near the REXOR site. The applicant argues that releases from REXOR are currently close to zero and will have no environmental impact.

While SEAC notes that it is not possible to establish a safe level of releases since a threshold level for the endocrine disrupting properties has not been demonstrated, the applicant has provided contextual information indicating that the environmental impact of the use applied for is limited. SEAC does not see a reason to disagree with the applicant's conclusions.

5.2. Benefits of continued use

Non-use scenario

According to the applicant, the most likely non-use scenario is that it would cease the production of all HYDRAGEL® kits, commercialised by the applicant, and not just the 142 kits associated with the use applied for. The applicant states that given the turnover of the products associated with the use applied for (40 % of Sebia'sturnover) and because the kits concerned with use 1 are heavily interrelated with other aspects of the applicant's business, it is foreseen that in the non-use scenario, production for the whole electrophoresis range would cease because the applicant would not be able to absorb such a loss. This would result in the closure of all of the applicant's sites, divisions and subsidiaries.

The applicant also 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 and high level of staff know-how. The applicant also mentions that relocation or subcontracting outside the EU would generate huge financial impacts but these are not quantified. Furthermore, the applicant states that relocation or sub-contracting of HYDRAGEL® kits outside the EEA would not be possible as there is a contractual commitment of shareholders controlled by the French Ministry of Finance to keep the production in France. In response to SEAC questioning, the applicant explains that this is a confidential agreement that was granted because of the applicant's contractual relations with public hospitals (including military hospitals) that meant the company was classified as strategic by the French State. As such, financial investors have been forced to make commitments not to relocate the company, activity and continuity of supply contracts.[13]

[13] While the applicant does have a presence outside the EU, the applicant explained during the trialogue that these are distribution only sites at which production would not be possible.

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

- the use would be taken up by market actors operating inside the EU (in the long term), or
- the use would be taken up by market actors operating outside the EU (in the long term)

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

- At least 133 jobs would be lost in the European Union

Benefits of continued use

Although the applicant states that the benefits of authorisation would impact all sites, divisions and subsidiaries, the economic impacts are estimated only for the 142 kits related to the use applied for. According to the applicant, the non-use scenario would not have a critical impact on its subcontractor REXOR. Therefore, the socio-economic analysis considers only the impacts on Sebia. The applicant assesses three main categories of impacts: economic impacts to the applicant and its supply chain, medical impact on patients, and the unemployment impact on staff employed by the applicant.

Economic impacts

The applicant argues that it is very unlikely that its competitors would be able to compensate the market loss in the short or medium term. This is due to the applicant's large market share (nearly 95 % of the European electrophoresis market), the high level of know-how required, the monopoly of the applicant for certain tests concerning the diagnosis of rare diseases and the capital-intensive production of IVD products.

The applicant bases the economic impact on losses of revenues over the 12-year requested review period. Based on an average annual revenue of €81 million in recent years and the foreseen growth over the review period, the applicant concludes that it would lose a total of €1.5 billion over 12 years (NPV in 2018, discount rate 4 %). The applicant states that it has seen its results grow by 8 % per year since 2017. Its business model, which is based on investments and what the applicant describes as "current developments" in the company is also based on a growth rate of 8 % per year.[14] As SEAC has not seen evidence to suggest that such a profit rate can be/has been realised for the HYDRAGEL® kits concerned with the use applied for, it is unable to conclude as to whether the assumption of a constant growth rate of 8 % is appropriate.

SEAC also notes that the economic impact assessment should focus on profit rather than revenue losses because this recognises that both revenues and costs can vary in response to changes in output. In response to SEAC questioning, the applicant, provided supplementary

[14] The applicant states that a growth rate of below 8 % would no longer ensure viability of the company.

information indicating that between 2015 and 2018, profits before tax represented 0-10 % of sales. The applicant estimates that lost profits in one year alone (taken to be 2022) would be in the range of €60-70 million. SEAC notes, however, that the profit information is inconsistent with annual revenue estimates of approximately €80 million (based on 2015-17 data) outlined in the application for authorisation (even when considering expected annual growth of 8 %). In addition to the quantified impacts, the applicant states that the non-use scenario would have a significant knock-on effect on the sales of other ranges in the applicant's portfolio as the relevant assays of the HYDRAGEL® range are a major prerequisite in accessing calls for tender, thus, potentially closing several markets to the applicant for several years. Other economic impacts that are discussed qualitatively are possible contract penalties linked to range discontinuation and the impacts on other actors in the value chain e.g. packaging and electronic suppliers as well as IVD device distributors.

Medical impacts

The concerned products are used in the diagnosis of a broad range of pathologies based on blood protein anomolies and are applied in medical specialities such as internal medicine, paediatrics, cardiology, oncology and gastro-enterology. According to the applicant, the products are integrated as a crucial step in the global diagnosis system, helping in the establishment of medical diagnostics or the follow-up of treatments. The concerned assays are used for chronic diseases where the number of patients is potentially very large as well as for rare and difficult to diagnose diseases such as Waldenström disease or Multiple Myeloma.

The kits associated with the use applied for enable earlier detection of the pathologies that in turn result in decreased mortality and in the reduction of costs related to treatment, hospitalisation and work absences. According to the applicant, almost 340 000 kits concerned by the use applied for were sold in 2017, corresponding to almost 84 million IVD tests.

The HYDRAGEL® kits have been specifically developed to be exclusively used on equipment provided by the applicant. Therefore, in order for hospitals, laboratories and other customers to change to the products of the applicant's competitors, they would need to also purchase new equipment and re-train personnel. In addition, hospitals and laboratories usually have global contracts that would need to be re-tendered. With 16 000 of the applicant's equipment units installed worldwide, the applicant claims that it is unlikely that competitors would be able to meet market demands. On the other hand, SEAC notes that the applicant also states that it does not have any information about the capacity of competitors or the substances that they use. Thus, it remains a possibility that competitors could supply the market in the case of non-authorisation, (and thus, redistributing some proportion of the applicant's revenue/profit losses) although the public consultation did not provide any evidence that this is the case. In any case, SEAC finds it credible that competitors would not be able to take over the applicant's market share in the short or medium term due to the applicant's large market share, the high performance demands on the products and the regulatory requirements.

Unemployment impacts

In presenting the unemployment impacts, the applicant argues that the cease of production of gel electrophoresis assays would in fact lead to the forced closure of the applicant and its subsidiaries. Hence, even if only 133 jobs are identified as directly and exclusively dedicated

to this use applied for, the applicant assumes that all 550 jobs at SEBIA and its subsidiaries 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 €101.7 million. The second approach, also endorsed by SEAC, applies the methodology proposed by Dubourg (2016)[15]. Using the latter method, the applicant calculates a cost of around €57.9 million over the requested review period, 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. SEAC understands that the cost of job losses estimated by the applicant includes staff both within and outside the EEA. If the assessment were to apply only to the 133 jobs associated with the use applied for), the social cost would be €14 million based on the Dubourg (2016) method used by the applicant. SEAC notes however, that this would underestimate the social cost within the EEA as it is likely that jobs would also be lost in the applicant's other European sites and subsidiaries.

Table 5: Socio-economic benefits of continued use

Description of major impacts	**Quantification of impacts**
1. Benefits to the applicant(s) 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 applicable
1.2 Avoided profit loss due to ceasing the use applied for	Not available
1.3 Avoided relocation or closure cost	Not applicable
1.4 Avoided residual value of capital	Not applicable
1.5 Avoided additional cost for transportation, quality testing, etc.	Not applicable
Sum of benefits to the applicant(s) and / or their supply chain	
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	€14 million
2.2 Foregone spill-over impact on surplus of alternative producers	Not available
2.3 Avoided consumer surplus loss (e.g. because of inferior quality, higher price, reduced quantity, etc.)	Not available
2.4 Avoided other societal impacts (e.g. avoided CO_2 emissions or securing the production of drugs)	Not available
Sum of impacts of continuation of the use applied for	
3. Aggregated socio-economic benefits (1+2)	€14 million

[15] https://echa.europa.eu/documents/10162/13555/unemployment_report_en.pdf/e0e5b4c2-66e9-4bb8-b125-29a460720554

5.3. Combined assessment of impacts

The applicant assesses that the monetised costs of the non-use scenario would be approximately €1.6 billion over the review period 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 to be €129 million. SEAC is unable to estimate the monetised impact in terms of profit.

The applicant also presents a cost-effectiveness analysis. Based on the quantified annual costs of the non-use scenario (lost revenue plus the costs of unemployment in 2022), divided by the expected annual substance release (0.03 kg of 4-tert-OPnEO), the applicant concludes that the cost-effectiveness is €4.3 billion per kg of 4-tert-OPnEO released.

Table 6: Socio-economic benefits and risks of continued use

Socio-economic benefits of continued use		**Excess risks associated with continued use**	
Benefits	€14 million	Monetised excess risks to workers directly exposed in the use applied for	Not applicable
Quantified impacts of the continuation of the SVHC use applied for on other actors	Not available	Monetised excess risks to the general population and indirectly exposed workers	Not applicable
Additional qualitatively assessed impacts	Availability of electrophoresis kits for the diagnosis of chronic diseases (characterised by e.g. enzymatic dysfunction or overproduction) and for rare and difficult to diagnose diseases, such as Waldenström disease or Multiple Myeloma. Almost 340 000 kits concerned by the use applied for are sold annually, corresponding to almost 84 million IVD tests. Delayed diagnosis could increase mortality and treatment costs. The costs to hospitals and laboratories have not been quantified but are likely to be considerable.	Additional qualitatively assessed risks	30 g/year (monitoring) or 4.4 kg/year (ERC)
Summary of socio-economic benefits	**€14 million** **Other qualitatively assessed impacts**	**Summary of excess risk**	**30 g/year (monitoring) or 4.4 kg/year (ERC)**

Table 7: Cost of non-use per kg

	Review period
Total cost (€)	€14 million
Total emissions (kg)	0.03-4.4
Ratio (€/kg)	€0.3-39 million per kg

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
3. "Ratio" = Total cost/Total emissions

5.4. SEAC's view on Socio-economic analysis

SEAC accepts the applicant's arguments that the options of relocating/subcontracting production or reducing product quality are not viable because of the qualification process that is required for the products, the demanding conditions on product performance that are necessary in the medical sector and the high level of staff know-how that is necessary to ensure that the end product is fit for purpose. SEAC also finds that the applicant's contract with the French ministry to keep production in France should be respected as this would generate financial and legal impacts if broken. SEAC, thus, considers that the non-use scenario of ceasing production of the affected HYDRAGEL® kits is credible. Given the applicant's large market share, the high performance demands on the products, the regulatory requirements, as well as taking into account the comments from the public consultation, SEAC finds it credible that competitors would not be able to take over the applicant's market share in the short or medium term. SEAC finds that in its initial application, the applicant overestimated the benefits of continued use, as it used revenue losses as the basis for assessing the economic impacts. While profit losses would be a more appropriate measure, SEAC is not able to use the profit information provided by the applicant to estimate changes to producer surplus. Therefore, the only quantified cost of the non-use scenario taken forward by SEAC is the social cost of unemployment which was estimated to be at least €14 million.

The qualitative descriptions of the use of the applicant's electrophoresis kits for the diagnosis of various diseases demonstrate the value of these products. With almost 340 000 kits concerned with the use applied for sold by Sebia in 2017, SEAC 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. The costs to hospitals and laboratories have not been quantified but are likely to be considerable, since the concerned kits have been developed to be exclusively used on equipment provided by the applicant.

In relation to the applican't cost-effectiveness analysis, which the applicant estimates for one year only, SEAC does not consider 2022 to be a representative year. Since 2022 represents the first year of unemployment in the applicant's assessment, the unemployment costs are, according to the applicant's calculations, disproportionally high in that year compared with the rest of the review period. Furthermore, the analysis is based on revenues, rather than profits. SEAC has recalculated the cost-effectiveness using the social cost of unemployment and the releases over a 12 year review period, giving a cost-effectiveness ratio of approximately €0.3-

39 million per kg released. Considering that this calculation does not take into account the economic or the medical impacts, the value can be considered conservative.

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 feasibility and economic viability of alternatives,
- any additional information provided by the applicant or its downstream users,
- 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 gave no advice on the lengths 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. Based on the information provided by the applicant, SEAC takes the following considerations into account:

- If the authorisation is granted, the applicant intends to pursue the substitution programme described in the application and recruit additional staff at an estimated cost of €9.3 million in order to substitute in 12 years.
- SEAC understands that the substitution phase could, in theory, be reduced to 7 years if additional staff was hired. However, SEAC finds it credible that, in comparison to a 12 year substitution, a 7 year substitution would imply higher recruitment costs as well as other potential costs and challenges related to finding and housing the required expertise. SEAC considers that the substitution timelines proposed by the applicant are reasonable considering the resources needed for the substitution and the high cost of reducing further the releases of 30 grams to 4.4 kg per year by not granting an authorisation.

- The products concerned with the use applied for are subject to high performance requirements and the possible alternatives would require specific legislative measures under the requirements regulating medical diagnostic devices in the various markets of the applicant.
- 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.

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

7. Proposed additional conditions for the authorisation

Were additional conditions[16] 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 the 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 and RMMs in the exposure scenarios.

8. Proposed monitoring arrangements for the authorisation

Were monitoring arrangements[17] proposed for the authorisation?

☐ Yes

☒ No

[16] 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.
[17] 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.

8.1. Description

None

8.2. Justification

As in section 7.

9. Recommendations for the review report

Were recommendations for the review report made?

☒ Yes

☐ No

9.1. Description

RAC recommends the applicant to further assess in any review report the feasibility to collect the remaining liquid waste from washing the glassware at the site of Lisses (SEBIA) for adequate treatment and act on the outcome of the feasibility study.

RAC recommends that the applicant should monitor at least quarterly or 4 times per year 4-tert-OPnEO and its principal degradation products in the waste water prior to release to the off-site WWTP at the site of Lisses (SEBIA) using an analytical method capable of adequately characterising the substance and its degradation products in water at an appropriately low level of quantification. The results should be included in any review report, including details of sampling point, the analytical method, the concentrations detected and the corresponding environmental release values.

9.2. Justifications

RAC observes that relevant solid and liquid wastes are collected for treatment or for incineration. The only waste water with residual 4-tert-OPnEO that is released without treatment to the sewage system results from washing of the glassware at the site of Lisses. RAC recommends the applicant to further assess in a potential review report the feasibility to collect these remaining liquid wastes.

The measurement results provided at least quarterly or 4 times per year should allow the evaluation of the effectiveness of the OCs and RMMs in place and to confirm that emissions are reduced to as low a level as is technically and practically possible. The frequency of the measurements should be sufficient to capture the variability in concentrations of the substance and its degradation products in the waste water (e.g. due to changes or operational fluctuations in the process).

10. Comments on the draft final opinion

Did the applicant(s) provide comments on the draft final opinion?

☒ Yes

☐ No

10.1. Comments of the applicant(s)

Was action taken resulting from the analysis of the comments of the applicant(s)?

☒ Yes

☐ No

☐ Not applicable – the applicant(s) did not comment

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

In their comments on the draft opinion, the applicant submitted a substitution plan. The information on the factors affecting substitution and the list of actions and timetables with milestones had already been provided in the AoA/SEA as part of the initial application, with additional clarifications provided in response to SEAC's questions. However, the section on monitoring of the implementation of the substitution plan was only provided in the comments on the draft opinion. With this new information, SEAC changed the opinion to state that a substitution plan had been provided.

An addition was also made to section 4.1, highlighting that the alternatives identified by third parties need to be assessed as the applicant is seeking a long-term alternative and would like to avoid any regrettable substitution. Additionally, a few editorial changes were incorporated based on the applicant's comments.

The applicant submitted an update of the CSR to reflect the RMMs and OCs implemented to minimise emissions as described in their responses to RAC and SEAC questions during the development of the opinion, and this information has been reflected in the opinion.

10.3. Reasons for not amending the opinion

In their comments on the draft opinion, the applicant stated that they will monitor quarterly the substance using a new method allowing the measurement of 4-tert-OPnEO and all the degradation products. This quarterly monitoring will be performed at Lisses (SEBIA) and Roma (INTERLAB) during the first year of the review period. Then, according to the applicant, the frequency will be adjusted at one time per year if the concentration of the substance and all its degradation products is below the limit of quantification of the method employed. The applicant expressed their concern about the cost of monitoring (estimated by the applicant at €40 000 for the validation of the method and €10 000 per site and year for quarterly monitoring). However, according to RAC, monitoring of the substance in the waste water quarterly or at least 4 times per year is required to capture the variability of the process and confirm that emissions are minimised as far as technically and practically possible. Therefore, the opinion has not been amended as suggested by the applicant.