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):

Professional use as a surfactant, in wash buffer components used in conjunction with Fluorescence In Situ Hybridisation (FISH) test kits and/or their Laboratory Developed Test (LDT) equivalents, in clinical diagnostic use for medical analysis of human tissue and blood samples to identify characteristic genetic abnormalities related to specific disease conditions

Submitting applicant

Abbott Diagnostics GmBH

ECHA/RAC/SEAC: AFA-O-0000006764-66-01/D

Consolidated version

Date: 19/05/2020

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[1]	**Abbott Diagnostics GmBH** (position in supply chain: upstream)
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 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 - effects to the environment
Use title	**Professional use as a surfactant, in wash buffer components used in conjunction with Fluorescence In Situ Hybridisation (FISH) test kits and/or their Laboratory Developed Test (LDT) equivalents, in clinical diagnostic use for medical analysis of human tissue and blood samples to identify characteristic genetic abnormalities related to specific disease conditions.**
	Other connected uses: not applicable
	Same uses applied for: not applicable
Use performed by	☐ Applicant ☒ Downstream User(s) of the applicant
Use ID (ECHA website)	0168-01

[1] 'Applicant' - includes also 'Authorisation Holder(s)' in case of the review report

Reference number	11-2120816695-47-0001
RAC Rapporteur RAC Co-rapporteur	João CARVALHO Irina KARADJOVA
SEAC Rapporteur SEAC Co-rapporteur	Christos ANASTASIOU
ECHA Secretariat	Mercedes MARQUEZ-CAMACHO Sandrine LEFEVRE-BREVART Romain FIGUIERE

PROCESS INFORMATION FOR ADOPTION OF THE OPINIONS

Date of submission of the application	20/05/2019
Date of payment, in accordance with Article 8 of Fee Regulation (EC) No 340/2008	01/08/2019
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
Public Consultation on use, in accordance with Article 64(2): https://echa.europa.eu/applications-for-authorisation-previous-consultations	14/08/2019-09/10/2019
Comments received	☐Yes ☒No Link: https://echa.europa.eu/applications-for-authorisation-previous-consultations/-/substance-rev/23847/del/200/col/synonymDynamicField_302/type/asc/pre/2/view
Request for additional information in accordance with Article 64(3)	On 16/09/2019 and 21/10/2019 Link: https://echa.europa.eu/applications-for-authorisation-previous-consultations/-/substance-rev/23847/del/200/col/synonymDynamicField_302/type/asc/pre/2/view
Trialogue meeting	Not held – no need for additional information/discussion on any technical or scientific issues related to the application from the rapporteurs
Extension of the time limit set in Article 64(1) for the sending of the draft opinions to the applicant	☐Yes, by [date] ☒No
The application included all the necessary information specified in Article 62 that is relevant to the Committees' remit.	☒Yes ☐No Comment:

Date of agreement of the draft opinion in accordance with Article 64(4)(a) and (b)	RAC: 13/03/2020, agreed by consensus
	SEAC: 05/12/2019, agreed by consensus
Date of sending of the draft opinion to applicant	11/05/2020
Date of decision of the applicant not to comment on the draft opinion, in accordance with Article 64(5)	19/05/2020
Date of receipt of comments in accordance with Article 64(5)	Not relevant
Date of adoption of the opinion in accordance with Article 64(5)	RAC: 19/05/2020, adopted by consensus.
	SEAC: 19/05/2020, 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 or its downstream users 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 **not** appropriate and effective[2] in limiting the risk. The proposed additional conditions for the authorisation are expected to result in operational conditions and risk management measures that are appropriate and effective in limiting the risk.

The use applied for may result in 12.5 kg per year of total emissions of the substance to the environment across 100-1 000 sites in the EU.

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, 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 to the REACH Regulation.

The following alternatives have been assessed (see Section 4 of the Justifications):

1. Removal/alteration of the role of 4-tert-OPnEO in the wash buffer of FISH assays
2. Substitution of FISH with an alternative technique
    a. Immunohistochemistry (IHC)
    b. Qualitative Real time Polymerase chain reaction (qPCR)
    c. Next Generation sequencing (NGS)
3. Substitution of 4-tert-OPnEO with alternative surfactants
    a. 20 alternative surfactant types were initially identified by the applicant.
    b. Eight alternative surfactant types were deemed to meet the non-ionic properties and other properties closely matching those of 4-tert-OPnEO.
    c. A final ranking of these eight alternatives produced a short list of three surfactants that could potentially act as an alternative for 4-tert-OPnEO in FISH post-

[2] 'Appropriateness' – relates to the following of the principles of the hierarchy of controls and compliance with the relevant legislation: '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.

hybridization wash buffer and for which feasibility testing will be undertaken. These alternatives are listed in Table A:

Table A. Final shortlist surfactants for feasibility testing and hazard screening

Screening ID	CAS No.	Surfactant category	Hazardous properties
1	68131-40-8	Alcohol Ethoxylate	Aquatic Chronic 3; H412: Harmful to aquatic life with long lasting effects.
2a	9005-64-5	Polyoxyethylene sorbitan monolaurate' (Polysorbate 20)	Not Classified
6	60828-78-6	Diol ethoxylate	Skin Irrit 2; H315

SEAC concluded on the analysis of alternatives and the substitution plan 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(s) or their downstream users.
- 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 €12 million and additional important benefits to society have been assessed qualitatively but have not been monetised, including:
    - Avoided loss of profits for downstream users and drug manufacturers using the applicant's systems.
    - Avoided costs in clinical trials and regulatory approvals for drug manufacturers.
    - Avoided delays in the diagnosis of cancer and other diseases and prescription of less effective therapies for a number of patients (over 400 000 FISH tests are conducted annually in the EU).

- 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, or
- 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]

- 10-100 jobs could be lost

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

PROPOSED CONDITIONS AND MONITORING ARRANGEMENTS, AND RECOMMENDATIONS

Additional conditions for the authorisation are proposed. These are listed in section 7 of the justification to this opinion.

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 a **7-year** review period is recommended for this use.

SUMMARY OF THE USE APPLIED FOR

Role of the applicant in the supply chain	Upstream ☐ manufacturer ☒ importer ☐ only representative ☐ formulator Downstream ☐ downstream user
Indicative number and location of sites covered	100-1 000 diagnostic laboratories, private diagnostics laboratories and hospital based and academic institutions located in EU.
Annual tonnage of Annex XIV substance used per site (or total for all sites)	Range per downstream user site: 0.10-0.55 kg/year of 4-tert-OPnEO Range for all EU downstream user sites: 10-100 kg/year of 4-tert-OPnEO
Function(s) of the Annex XIV substance.	4-tert-OPnEO is present as a surfactant in the wash buffers of FISH Assay kits, to wash unbound probe DNA and other unbound biological components originating from the specimen, including proteins from microscope slide on which the samples are prepared. Removal of unbound components is required to eliminate critical non-specific signal to ensure the precision, accuracy and specificity of the test.
Type of products (e.g. articles or mixtures) made with Annex XIV substance and their market sectors	Use as a surfactant, in a wash buffer components used in conjunction with an In Vitro Diagnostic Device, FISH test kits and/or their Laboratory Developed Test equivalents, in clinical diagnostic use for medical analysis of human biological samples.
Shortlisted alternatives discussed in the application	Alternative substances considered: - Alcohol Ethoxylate (CAS: 68131-40-8) - Polyoxyethylene sorbitan monolaurate (EC: 500-018-3, CAS: 9005-64-5) - Ethoxylated acetylenic diols (CAS: 9014-85-1)
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 if 'No' – which endpoints are not addressed
Adequate control demonstrated by applicant for the relevant endpoint(s)	☐Yes ☐No ☒Not Applicable – non-threshold substance
Level of release used by applicant for risk characterisation	<u>Environment:</u> Air: 0 Kg/year. Emissions to air are considered to be null, because the substance is not volatile at the operating temperatures. Water: *Downstream user site releases*: 0.10 kg/year of 4-tert-OPnEO for most users; up to 0.55 kg/year of 4-tert-OPnEO for the largest-volume user. *Local releases*: 0.10 to 1.70 kg/year of 4-tert-OPnEO depending on the local area (i.e grouping of individual downstream user sites by geographical area assuming their releases would enter the same sewage system – 23 different local areas). *Total EU releases*: 12.5 kg/year of 4-tert-OPnEO Soil: 0 kg/year. No direct releases to soil take place during use of IVD kits.
Risk Characterisation	Environmental compartments: The applicant did not attempt to derive PNECs or RCRs. The CSR describes a worst case scenario considering that all 4-tert-OPnEO in use is released at the downstream users' sites. The OCs and RMMs as described in the Exposure Scenario do not prevent or minimise releases to the environment as far as technically and practically possible.

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)	7 years
Most likely Non-Use scenario	The Applicant will stop supplying the EU market with FISH Assay kits after the Sunset Date.
Applicant conclude(s) 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	€1-10 million over 7 years
Society's benefits of continued use	At least €12 million over 7 years. Avoided delays in the diagnosis of cancer and other diseases and prescription of less effective therapies for a number of patients (over 400 000 FISH tests are conducted annually in the EU).
Monetised health impact on workers	Not applicable
Distributional impacts if authorisation is not granted	-
Job loss impacts if authorisation is not granted	€1-10 million over 7 years (10-100 jobs could be lost)

SUMMARY OF RAC AND SEAC CONCLUSIONS[4]

1. Operational Conditions and Risk Management Measures

1.1. Conclusions of RAC

Conclusion for environment

As there is no requirement in the Exposure Scenario (ES) for downstream users to collect liquid and solid waste for adequate treatment, RAC concludes that the operational conditions (OCs) and risk management measures (RMMs) described in the application are **not** appropriate and effective in limiting the risk.

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 exposure estimates provided by the applicant are appropriate.

Does RAC propose additional conditions[5] related to exposure assessment for the authorisation?

☐Yes ☒No

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

[5] Conditions can 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.

Does RAC propose monitoring arrangements[6] 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

The applicant has treated 4-tert-OPnEO as a non-threshold substance and did not 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[7] and RAC's conclusion at the 50th meeting that it is currently not possible to determine a threshold for the ED properties of this substance.

Based on the OCs and RMMs described in the ES, notably the absence of a requirement to collect all relevant liquid and solid waste for adequate treatment, RAC is of the view that the applicant has not 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 12.5 kg/year emissions of 4-tert-OPnEO to the environment across 100-1 000 sites in the EU.

4. Analysis of alternatives and substitution plan[8]

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

10-100 kg/year of 4-tert-OPnEO

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

☐Yes ☒No

[6] 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.

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

[8] 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

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

☒Yes ☐No

Conclusions of SEAC

The alternatives identified by the applicant are not technically and economically feasible by the sunset date. The substitution plan proposed by the applicant is credible and feasible.

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 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,
- SEAC's assessment of the comments received in the public consultation,
- 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

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

SP ☐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 ☒Not applicable

JUSTIFICATIONS

0. Short description of use

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

FISH kits are used by medical laboratories and clinics in the EU for diagnosing cancer and determining the type of cancer of a patient. 4-tert-OPnEO is only contained in the post hybridisation wash buffer used to support Fluorescence In Situ Hybridisation (FISH) testing in approximately 400 of the applicant assays, of which more than 100 are classified as IVDs (*In vitro* diagnostic device).

The applicant's EU customers are considered to be downstream users of 4-tert-OPnEO as contained within the FISH wash buffer.

The applicant offers FISH kit assay products for use in genetics and oncology. In both cases, the use of a typical FISH Assay includes the following steps: pre-treatment, hybridisation, post hybridisation wash, counterstain and examination. It is during the post hybridisation wash that 4-tert-OPnEO is used to wash the slide and remove the unbound probe.

FISH diagnostic products may be used in manual assays, or in partially automated assays where some slide processing steps may be performed using dedicated equipment (e.g. pre-treatment to remove excess protein and/or other cellular debris; co-denaturation and hybridisation of sample and FISH probe; post-hybridisation washes to remove unbound excess probe; raw microscopy data collection; and/or enumeration of final FISH imaged results).

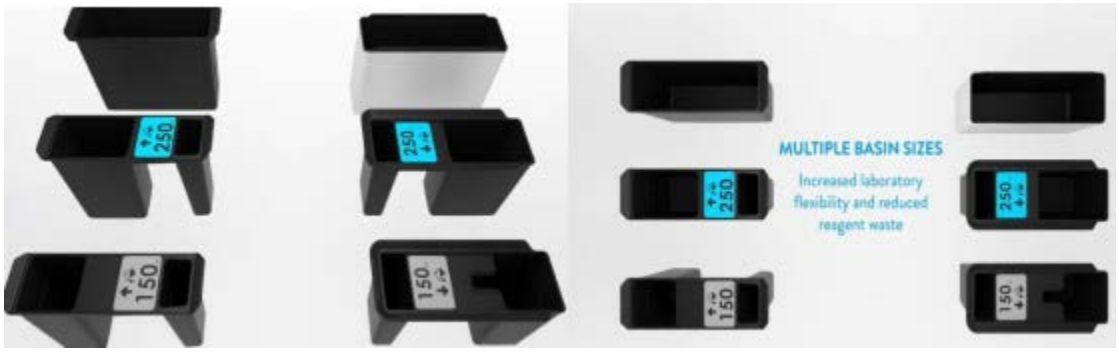
For manual operations (cf. Figure 1), the post hybridisation wash procedure (which contains the 4-tert-OPnEO) is likely to occur on the laboratory bench alongside a water bath. FISH assays tend to involve a lot of manual handling of the slides with the samples. When using semi-automated instrumentation, the applicant supplies the automated FISH testing platforms to make pre-hybridisation, hybridisation and post-hybridisation processing of slides more streamlined, and to substantially automate final FISH slide quality examination.

Figure 1: Wash procedure in manual operation (Coplin jars)

Source: Application for Authorisation

In the automated system, reagent basins are used for wash buffer solutions (Figure 2). The numbered reagent basins are each removed from the instrument, and then filled (or refilled) one at a time; to the appropriate depth needed for processing according to the processing map selected and the specific protocol provided in the reagent package insert. Upon completion of all required processing protocol(s) at end of day, used reagents in the basins must be disposed of.

Figure 2: Reagent bassins used for wash procedure in (semi)-automated systems



Source: Application for Authorisation - Images credited to the Applicant
https://www.molecular.abbott/int/en/products/instrumentation/vp-2000-processor-vip2000-processor

For both the manual and (semi)-automated systems described, all hazardous materials, including wash buffer components containing 4-tert-OPnEO, should be disposed of according to the institution's guidelines for hazardous disposal and in accordance with local regulations. Empty ambient reagent vessels may be cleaned with most detergent solutions, using a dampened cloth; then wiped a second time to rinse, using a cloth dampened with water. The heated reagent basins are made of stainless steel and should be cleaned with detergent or organic solvents whenever they are emptied.

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

4-tert-OPnEO is used as a surfactant in the wash buffers of FISH Assay kits, to wash unbound probe DNA and other unbound biological components originating from the specimen, including proteins from microscope slide on which the samples are prepared.

4-tert-OPnEO acts as a surfactant and wetting agent that aids in the removal of coverslips from hybridised microscope slides, promotes solubility of unhybridised (free) FISH probe, reduces nonspecific interactions between FISH probe and the cellular components present in human specimens, and minimises self-aggregation of the FISH probe as well as FISH probe co-aggregation with proteins or other specimen components.

The key substance properties of 4-tert-OPnEO that allow the system solutions to function according to the requirements include: surfactant classification (non-ionic); solubility, hydrophile-lipophile balance; surface tension; and stability of the wash buffer / cloud point.

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

The applicant is applying on behalf of its EU customers, hospitals and clinics for an authorisation for the continued use of 4-tert-OPnEO in FISH wash buffer.4-tert-OPnEO is contained in the post hybridisation wash buffer used to support FISH testing.

0.4. For upstream applications: Downstream User survey

The applicant has not initiated any downstream user survey to obtain information.

1. Operational Conditions and Risk Management Measures

A summary of the operational conditions (OCs) & risk management measures (RMMs) in the environmental contributing scenarios is provided below. The detailed conditions of use are available from section 9.1 of the chemical safety report (CSR).

No working contributing scenarios are presented, as the scope of the CSR is limited to the environmental risk of 4-tert-OPnEO.

No contributing scenario for the service life is provided because it is not relevant: the use is an end-use (i.e. after their use the kits are disposed as waste).

1.1. Environment

The applicant presented one Exposure Scenario - ES1 - Professional use of wash buffer containing 4-tert-OPnEO to be used with final test kits at laboratory scale with less than or equal to 1 litre or 1 kg present at workplace - with one environmental contributing scenario: (ERC 8a - Widespread use of non-reactive processing aid (no inclusion into or onto article), indoor.)

Operational Conditions and Risk Management Measures in place for control of emissions to all compartments:

Operational conditions

- Daily use amount per downstream user site: 0.00042 kg of 4-tert-OPnEO for most users; up to 0.0021 kg of 4-tert-OPnEO for high users
- Number of days of release per year: 260 days
- Concentration of 4-tert-OPnEO in the washing buffer: 0.1 to 0.3 %
- Maximum operating temperature: 73 °C

Technical and organisational conditions and measures

As common organizational measures, the following are relevant: on board solutions and instruments are handled only by trained professional clinical technicians, technical training is developed and guidance material is available. Additionally, product manuals, safety data sheets (SDS) and instructions for use are also accessible and give information related with the RMMs in place. More detailed information regarding technical and organizational RMMs available for minimizing release to water is described in Table 1.

Waste management

The waste containing 4-tert-OPnEO are generated from the following activities:

- Used wash buffer in manual or (semi)-automated assay (liquid waste)
- Used microscope slides (solid waste)
- Contaminated single use containers (e.g Coplin jars), empty wash buffer bottles and clean up materials (liquid and solid waste)

- Residues from equipment cleaning (liquid waste)
- Expired/unused wash buffer (liquid waste)
- Spillage (liquid and solid waste)

It is assumed by the applicant that downstream users release the liquid waste to wastewater which is connected to the facility wastewater stream. Therefore, all liquid waste containing the substance is assumed to be released to the wastewater and treated in a municipal Sewage Treatment Plant (STP) before it is discharged to the environment.

Considering solid waste, the applicant clarified that the used microscope slides are disposed of as hazardous waste and incinerated as they have been in contact with potentially cancerous tissue or blood cells. Regarding the other solid waste (e.g. contaminated single use containers, empty wash buffer bottles and clean up materials), the applicant indicates that, based on information received from some downstream users, this waste may also be collected and sent for incineration.

Based on the above, and not having conducted any downstream user survey, the applicant assumes that the RMMs have 0 % efficiency.

Table 1: Environmental RMMs - summary

Compartment	RMM	Stated Effectiveness
Water	Technical: - Laboratory setting. - Use of wash buffers loaded onto the instrument in designed wash basins. - Use of automated steps to limit and control manual intervention. - Use of ready to use solution to minimise the need for dilution task. Organisational: - Wash buffers and instruments are handled only by trained professional clinical technicians. - Technical training, guidance material, product manuals and instructions for use and waste management. - Downstream users are advised on optimisation of test batching in order to reduce liquid waste generation.	0 % efficiency is assumed by the applicant (worst case scenario considering that all used 4-tert-OPnEO is released to the wastewater system).

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

The applicant mentioned that all hazardous materials, including wash buffer components containing 4-tert-OPnEO, should be disposed of according to the institution's guidelines for hazardous disposal in accordance with local, state and federal regulations. This results in the application of different management measures for liquid and solid wastes, depending on the country where the downstream users are located.

Therefore, the applicant assumes that all the liquid waste containing the substance is released to the wastewater and treated in a municipal STP along with liquid waste from other users before it is discharged to the environment.

Regarding the solid waste, there is no confirmation that the collection for adequate treatment is performed at all the downstream user sites, particularly for contaminated single use

containers, empty wash buffer bottles and clean up materials.

Based on the above, and not having conducted any downstream user survey, the applicant assumes that the RMMs already in place have 0 % efficiency, and that 100 % of the 4-tert-OPnEO sold to and used at a downstream site is discharged into the wastewater and treated in a municipal STP.

1.3. Conclusions on OCs and RMMs

The OCs and RMMs described in the ES are **not** appropriate and effective in limiting the risk to the environment.

Overall conclusion

Are the operational conditions and risk management measures appropriate[9] and effective[10] in limiting the risk for workers, consumers, humans via environment and / or environment?

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

Concerns related to OCs and RMMs lead to additional conditions for authorisation presented in section 7. Additionally, recommendations for the review report are presented in section 9.

2. Exposure assessment

2.1. Environmental emissions

Air

The substance is not volatile, and all slide washing operations take place at temperatures of approximately 73 °C or 22 °C in closed containers for approximately two minutes for each wash step. The vapour pressure of 4-tert-OPnEO is lower than 2 Pa at 22 °C. Therefore, the applicant considers null emissions for air compartment.

Water

Given the large number and widespread distribution of professional end users and lack of uniform criteria to handle these type of waste, the applicant considers the worst case approach to release estimates by assuming that all quantities of FISH Assay wash buffer solutions distributed within the EU/EEA are released to the environment either through the discarding of residual quantities and other unused material or through the instrument liquid waste stream which are discarded to wastewater.

This includes also the wash solutions used in the manual or automated FISH Assay that must be discarded at the end of each day. Unused pre-formulated wash solutions supplied to customers by the applicant must be discarded after one year, or sooner if solution appears

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

cloudy or contaminated. If, however, the unused wash solutions were prepared on-site by the customer, then the unused amount must be discarded after six months, or sooner if the solution appears cloudy or contaminated.

Soil

The applicant considers that no direct releases to soil take place during the use of IVD kits.

Table 2: **Summary of environmental emissions**

Release route	**Release factor**	**Release per year** (tonnes or kilograms)	**Release estimation method and details**
Air	0 %	0	The substance is not volatile at the operating temperatures.
Water	100 %	Site release rate: 0.10 kg/year of 4-tert-OPnEO for most users; up to 0.55 kg/year of 4-tert-OPnEO for the largest-volume users. Local release rate: 0.10 to 1.70 kg/year of 4-tert-OPnEO depending on the local area (i.e. grouping of individual downstream user sites by geographical area assuming their releases would enter the same sewage system – 23 local area). Total EU release rate: 12.5 kg/year of 4-tert-OPnEO	It is assumed, as a worst case, that all quantities of buffer containing 4-tert-OPnEO distributed in the EU are released directly to the facility's wastewater system and from there to the local sewage system. It is assumed that there are no environmental release controls in place.
Soil	0 %	0	No direct releases to soil take place during the use of IVD kits.

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

The applicant has not conducted any downstream user survey, and assumes that the RMMs already in place have 0 % efficiency, and that 100 % of the of 4-tert-OPnEO used at a downstream site is discharged to the wastewater.

This leads to a worst case estimate of the releases to the aquatic environment both at downstream user sites, and in the EU.

2.3. Conclusions on exposure assessment

RAC considers that the release estimates (zero effectiveness of RMM's and 100 % release) provided by the applicant are a worst case scenario.

RAC did not evaluate the predicted environmental concentrations (PECs) provided by the applicant since 4-tert-OPnEO is treated as a non-threshold substance with regard to 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.

3. Risk characterisation

The applicant has treated 4-tert-OPnEO as a non-threshold substance and did not 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[11] and RAC's conclusion at the 50th meeting that it is currently not possible to determine a threshold for the ED properties of this substance.

Based on the OCs, the lack of RMMs described in the exposure scenario, notably the absence of a requirement to collect all relevant liquid and solid wastes for adequate treatment, RAC is of the view that the applicant has not 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 12.5 kg/year total emissions of 4-tert-OPnEO to the environment across 100-1 000 sites in the EU.

4. Analysis of Alternatives and substitution plan[12]

The applicant is applying for an authorisation on behalf of its EU customers, which are considered downstream users under REACH. The type of laboratories typically supplied by the applicant includes reference diagnostic laboratories, private diagnostics laboratories as well as hospital-based and academic institutions.

What is the amount of substance that the applicant's downstream users use per year for the use applied for?

10-100 kg in total (exact figure claimed confidential). Typical downstream users use up to 0.10 kg per year while the largest users may use up to 0.55 kg per year.

4.1. Summary of the Analysis of Alternatives and substitution plan by the applicant and other information available

The applicant has examined the following three potential classes of alternatives:

- Removal/alteration of the role of 4-tert-OPnEO in the wash buffer of FISH assays
- Substitution of FISH with an alternative technique
- Substitution of 4-tert-OPnEO with alternative surfactants

The classes of alternatives were discussed in terms of the following key product performance requirements/indicators:

1. Precision

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

[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*".

2. Analytical/clinical sensitivity
3. Clinical specificity
4. Reduction of unwanted interactions of FISH probe with specimen matrix
5. Reduction of FISH probe non-specific background

A brief introduction to each potential class of alternatives is presented below:

1. Removal/alteration of the role of 4-tert-OPnEO

A series of laboratory tests conducted by the applicant attempted to assess the impact that eliminating or reducing the concentrations of 4-tert-OPnEO would have on the performance of FISH assays. Results obtained indicated significant difficulties with the removal of the coverslips. Ease of coverslip removal ensures the target's unique cellular morphology remains, where the specimen may be compromised.

Hence the results indicated that this approach was unacceptable.

2. Substitution of FISH with an alternative technique

Concerning the possibility of substituting FISH with an alternative technique, the applicant focused their efforts on a thorough literature review of publically-available information on such possible technologies. The most significant alternatives identified and briefly presented in the analysis of alternatives by the applicant were the following:

a. Immunohistochemistry (IHC)
b. Qualitative Real time Polymerase chain reaction (qPCR)
c. Next Generation sequencing (NGS)

None of these technologies were deemed appropriate to substitute FISH, which is a highly versatile technique that cannot be easily substituted with a single alternative diagnostic method. The applicant explained that all alternative technologies have limitations that make them technically infeasible to substitute FISH as an essential technique in medical diagnostics. Table 3 provides a summary of the known limitations of each of the alternatives to FISH assays. Based on its evaluation of alternative diagnostic techniques, the applicant concluded that substitution at the level of technology is unsuitable and discarded this option.

Table 3: Limitations of identified possible alterative techniques to FISH

Technique	Description	Known limitations
Immunohistochemistry (IHC)	The technique targets antigens or haptens in cells by binding to antibodies. Binding is visualised in different manners, either by using fluorescence or dyes.	Requires the development of unique and specific antibodies. Subjective grading system could lead to errors.
Qualitative Real time Polymerase chain reaction (qPCR)	Amplifies the DNA to produce specific DNA fragments in situ: a rapid alternative to in situ hybridisation for mapping short, low copy number sequences without isotopes.	Requires tissue fixation methods-high dependence on tissue quality, extraction procedures and probe selection. Increased technological requirements
Next Generation sequencing (NGS)	A series of techniques that rapidly sequence an individual's DNA. Involves the preparation of the DNA, amplification using technique such as PCR followed by sequencing.	Early stages of development, potentially high cost, equipment and software. Multiple instruments to replace single FISH apparatus. Longer development times

3. Substitution of 4-tert-OPnEO with alternative surfactants

Instead, the applicant deemed the option to replace 4-tert-OPnEO in the FISH wash buffer with

an alternative surfactant to be most promising and conclusive pathway of substituting the SVHC.

By reviewing information on commercially available surfactants, the applicant initially identified a list of 20 surfactant types (alternatives) that were screened. The most significant properties, impacting product performance requirements, used to screen the potential of alternatives as suitable surfactants were the following:

1. Surfactant classification (i.e. non-ionic, ionic, anionic, zwitterionic)
2. Solubility
3. Hydrophilic Lipophilic Balance (HLB) value
4. Stability of wash buffer / Cloud point
5. Surface tension

Of the 20 surfactant types initially identified by the applicant, eight were deemed to meet the non-ionic properties and other properties closely matching those of 4-tert-OPnEO.

The selected eight alternatives were ranked based on how closely each one matches the 4-tert-OPnEO surfactant currently in use against HLB, cloud point and surface tension. Since several of the screening list surfactants fall within the acceptable ranges of the criteria proposed, the Applicant's claimed their previous experience with use of a surfactant as being of significance in the final stages of the short listing (claiming that proven experience and demonstrated feasibility in manufactured products allow comfort in known future supply, availability quality and performance of the surfactant).

The aforementioned ranking of these eight alternatives produced a short list of the following three surfactants that could potentially act as an alternative for 4-tert-OPnEO in FISH post-hybridization wash buffer:

1. Alcohol Ethoxylate (CAS No. 68131-40-8)
2. Diol ethoxylate (CAS No. 9014-85-1)
3. Polyoxyethylene sorbitan monolaurate (Polysorbate 20)(CAS No. 9005-64-5)

The shortlisted alternatives were tested against a series of criteria including specificity, background, intensity, and cross hybridization and they all produced acceptable results as a substitute to 4-tert-OPnEO in FISH wash buffer.

Polysorbate 20 was chosen as the most promising alternative for the use applied for, mainly because this substance has the least hazardous properties from the three substances shortlisted. Indeed, the selected substance is currently classified as non-hazardous and its use does not cause any environmental concern.

The applicant developed a comprehensive substitution and phase out plan for all the assays concerned. In order for the Applicant to verify that the identified alternative can be used successfully in the impacted FISH assays, a number of assessments and regulatory steps must be completed as follows:

1. Design Verification Phase - Duration: 37 months
2. Regulatory Approval Phase - Duration: 6-24 months
3. Implementation Phase - Duration: 36 months
4. Customer Conversion Phase - Duration: 37 months

Substitution activities were initiated in 2014, and these are expected to continue through the end of 2027. The 7-year review period requested by the applicant, necessary for the completion of the submitted substitution plan, takes into consideration any delays related to

the implementation of the EU In-Vitro Diagnostic Device (IVD) Regulation.

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 and its downstream users before the Sunset Date?

☐Yes ☒No

The applicant has identified a promising alternative surfactant (Polysorbate 20) to 4-tert-OPnEO for use in the wash buffer of FISH assays. A comprehensive substitution and phase out plan has been developed for all of the applicant's impacted assays, emphasizing the various regulatory steps that must be completed before this substitution can take place in accordance with the applicant's quality procedures. However, real-time stability studies are currently in progress, thus making it impossible for the applicant to already conclude whether Polysorbate 20 is a technically feasible alternative to 4-tert-OPnEO.

The substitution timing described by the applicant is credible and considers the assessments and regulatory steps that must be completed. The 7-year review period requested by the applicant is necessary for the completion of the substitution plan and takes into consideration possible delays associated with the implementation of the EU In-Vitro Diagnostic Device (IVD) Regulation.

The applicant concluded that the cost arising from the transition to the chosen alternative (€1.1m to €3.2m) is acceptable to them, meaning the transition to the identified alternative surfactant is economically feasible over the duration of the requested review period. This cost is attributed mainly to the extensive R&D costs as well as the necessary regulatory approval for approximately 400 assays.

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

SEAC considers that the applicant's approach to identifying and assessing alternatives allows for conclusions on the availability and suitability of alternatives. In SEAC's view, the applicant's assessment and focus on one alternative substance is justified considering its comparable performance to 4-tert-OPnEO in FISH assays.

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 1) the

required regulatory steps that must be completed for this substitution to take place, 2) the applicant's quality procedures, and 3) the real-time stability studies needed to ensure the performance of Polysorbate 20 in practice.

When challenged by SEAC on the possibility of the applicant developing and implementing a suitable alternative ahead of the requested review period of 7 years, the applicant substantiated the fact that the review period it sought is necessary because of regulatory review cycle times in various countries. In parallel, the applicant stated that any investment in acquiring additional human resources would not substantially reduce the timeline of the substitution.

The applicant claims that there is no path available for acceleration of the required regulatory approvals with the longest lead times, even if other activities (e.g. more than 2 000 document updates) were accelerated by increasing human resources. SEAC does not possess information that would challenge the applicant's claims in that regard.

4.4. Substitution activities / plan

The applicant has identified a promising alternative surfactant to 4-tert-OPnEO for use in FISH wash buffer; Polysorbate 20, which is currently classified as non-hazardous and hence its use should not cause any environmental concern.

Substitution activities are expected to continue for 7 years after the sunset date; through the end of 2027. According to the applicant, the following substitution steps, including assessments and regulatory steps must be completed:

1. Design Verification Phase - Duration: 37 months (commenced in 2018)

   The chosen potential alternative surfactant is required to be assessed within the design verification phase. The phase aims to verify that the product produced using the alternative substance continues to meet all potentially impacted product requirements. Within the design verification phase, stability of the product is considered the most critical performance requirement. Real-time stability studies are in progress on seven assays to verify design parameters. Stability testing is critical for the assay products to demonstrate that the product can meet the regulatory requirement to perform within its shelf life. It is not possible to move to the next phase of the substitution process until the stability is confirmed for all of the Applicant's approximately 400 assays. It should be noted that if any of the assays fail with the substituted surfactant, the Applicant will return to the shortlisted surfactants and repeat the studies until stability is confirmed.

2. Regulatory Approval Phase - Duration: 6-24 months

   Approval from regulatory bodies is necessary to ensure the conformity of the product with the relevant quality, safety and efficacy regulations in each of the countries where the product is marketed. The Applicant markets FISH products in 64 different countries. In a regulatory impact assessment, the Applicant has identified the change as being 'significant' in all markets. Extensive documentation is required to be compiled on each product and submitted to multiple regulatory agencies across the world. Review times can be extensive, with some requiring up to 24 months. Once approval is obtained from all the impacted countries, the alternative substance can be implemented into the manufacturing process for commercial use. New rules on IVDs marketed in the EU/EEA are expected to become effective during this time. The Applicant allows for a 2.5-year contingency for impact of the change in regulation.

3. Implementation Phase - Duration: 36 months

   The implementation phase includes the scale up to full manufacture and involves significant activity related to change control procedures mandated by regulations, for this single change the Applicant must amend documentation for all 400 of its assays, including package inserts, kit labels and internal quality documents. This effort is significant and requires input across many functional areas. Documentation for all manufacturing, quality control testing, marketing, and medical writing must be updated prior to marketing the substitution FISH wash buffer.

4. Customer Conversion Phase - Duration: 37 months

   Upon commercial launching of the product, time must be allowed for customers to implement required changes to adopt the substituted FISH wash buffer. Customers may be required to validate the substituted buffer within their own quality procedures. Further to this validation, a 37-month shelf-life expiration timeframe allows for all existing FISH buffer containing 4-tert-OPnEO to be phased out by its customers.

Has the applicant submitted a substitution plan?

☒Yes ☐No

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

Polysorbate 20 is the potential alternative surfactant identified by the applicant. This is a commercially available, economically feasible alternative to 4-tert-OPnEO. Even though conclusions on technical feasibility of the identified alternative cannot be made before the completion of design verification studies, the applicant has presented a comprehensive substitution schedule.

SEAC understands that the phases of this substitution program are dictated by the internal quality procedure of the applicant, and by the regulatory approval and phase out processes that must be completed.

The substitution and phase-out of 4-tert-OPnEO in FISH wash buffer, in use by the applicant's customers in clinical laboratories, should be completed within 7 years from the sunset date. The time needed to substitute, per the applicant's claim, seems credible to SEAC.

SEAC understands that, if Polysorbate 20 fails to perform as expected in any of the model assays, the applicant will commence stability studies with the remaining shortlisted surfactants. To date stability has been verified for three of the seven model assays.

The substitution plan submitted seems credible and feasible. Moreover, SEAC considers that the applicant's approach to identifying and assessing alternatives is robust and allows for conclusions on the availability and suitability of alternatives.

Considering the alternative's comparable performance to 4-tert-OPnEO in FISH assays, SEAC finds justified the applicant's focus on one alternative surfactant (Polysorbate 20). The approach employed and the ensuing deductions leading to the identification of the one

alternative surfactant is detailed and valid.

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 1) the required regulatory steps that must be completed for this substitution to take place, 2) the applicant's quality procedures, and 3) the real-time stability studies needed to ensure the performance of the singled-out alternative surfactant in practice.

SEAC considers that the substitution plan (activities and timelines) proposed by the applicant is credible and takes into consideration possible delays associated with the implementation of the imminent (May 2022) EU In-Vitro Diagnostic Device (IVD) Regulation (which is to replace the current IVD Directive).

The applicant, in response to questions by SEAC, substantiated that the development and implementation of a suitable alternative ahead of the requested review period of 7 years is not feasible, primarily due to regulatory review cycle times in various countries.

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

The alternatives identified by the applicant are not technically and economically feasible by the sunset date. The substitution plan proposed by the applicant is credible and feasible.

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

Based on the average 2016-2018 use volumes of its products in the EU, the applicant estimates that the use of the substance results in annual releases of 12.5 kg of 4-tert-OPnEO to the environment. This amount represents a conservative estimate of future releases as the use volumes of 4-tert-OPnEO are expected to remain stable or slightly decline over the requested review period of 7 years (CSR, p.61). The use is spread over 100-1 000 individual laboratories and hospitals around the EU, meaning that the average emission of 4-tert-OPnEO to the environment per site and year is well below 1 kg.

According to the applicant, the IVD kits package inserts and the instrument operation manuals provide instructions for waste handling, including recommendations to ensure that waste disposal is performed in accordance with relevant local, state, and national regulations. However, the applicant notes that regulations vary significantly within the EU and, while some member states may allow direct disposal of the aqueous wastes to the general wastewater system, others may require disposal by incineration (CSR, p.77). The applicant states that no reliable information regarding downstream users' management of wastes is available to the company. It is assumed as an absolute worst-case approach that all liquid waste containing the substance is released to the wastewater stream.

RAC concludes that the use applied for may result in emissions to the environment of the total volume of 4-tert-OPnEO in use, equivalent to 12.5 kg per year across 100-1 000 sites in the EU.

5.2. Benefits of continued use

Non-use scenario

The applicant manufactures the FISH kits at their plant in Des Plaines, Illinois, in the US and sells the finished FISH kits with the wash buffer containing 4-tert-OPnEO to EU and non-EU customers. If an authorisation for the use of 4-tert-OPnEO-containing wash buffers in FISH tests is not granted, the applicant will not be able to sell their products to their EU customers (SEA, p.31). Therefore, the applicant assessed three non-use scenarios (NUS) in their application:

- NUS A: stop manufacturing of FISH assays altogether and shut down the manufacturing facility,
- NUS B: only stop manufacturing of FISH assay kits for EU customers and continue the other operations normally, and
- NUS C: partially adopt a promising alternative for some of the FISH products as soon as possible.

The share of EU sales to the applicant's global sales of FISH products is between 0-25 %. Although this figure is considered significant, the applicant states that shutting down the production because of a loss of 0-25 % of the total sales would not be realistic and on this basis discards NUS A. The applicant considers NUS B to be more likely. Under NUS B the facility in Des Plaines would reduce the production of FISH products to keep serving their non-EU customers. Although the applicant assumes that NUS C is also possible, it is not certain when a suitable alternative to 4-tert-OPnEO will become available.

Delays in supply of FISH assay kits will negatively impact the applicant's revenues and profits. The applicant therefore argues in its substitution plan that it will not be able before 2026 to take to the market first products using the most promising alternative in the wash buffer. This means that the impacts under NUS C will be almost the same as those under NUS B.

Additionally, the applicant states that it will be difficult to regain lost market shares because of a loss of credibility and customer loyalty to existing suppliers. Based on the products manufactured by the applicant and the markets they operate it, SEAC considers credible that NUS B would be the most likely should an authorisation not be granted.

The applicant is the market leader for FISH assays in the EU, holding 10-50 % of the EU market in 2017. Due to the high market share, it is likely that their competitors could not serve all their customers without interruptions. In consequence, this would decrease testing capacity for DNA aberrations for cancer and other genetic conditions in the EU. Further to the availability of competitor products, the applicant informs that it typically takes between 3 and 12 months before the applicant's customers can transition to an alternative supplier, depending on each laboratory's policy for validating new products.

SEAC notes that it is unclear whether alternative tests that do not use 4-tert-OPnEO/4-NPnEO would be available from competitors. If competitors' products also contain 4-tert-OPnEO/4-NPnEO at a level higher than 0.1 % w/w, then downstream users would similarly need an authorisation for the use of these products.

SEAC is not aware of competitive IVD systems for detecting genome abnormalities in humans which do not use OPE that would be readily available in the EU. No such information was brought forward to SEAC during the public consultation.

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

- The use would cease altogether, or
- The use would be substituted by market actors operating inside the EU, or
- 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?

- 10-100 jobs could be lost

Socio-economic impacts of continued use

The applicant is currently the largest supplier of FISH assay kits in the EU, holding a 10-50 % market share. FISH kits are used at laboratories, hospitals and research centres for diagnosing cancer, determining the type of cancer of a patient, and for prescribing Companion Diagnostics (CDx) therapies.

In case an authorisation for the use applied for is not granted, the applicant estimates that their profit losses during the 7-year review period requested would be €1-10 million (value discounted to end of 2021 prices, using an annual discount factor of 4 %). Some of the economic impacts are expected to occur outside the EU, as the applicant is based in the US.

In its assessment, the applicant considers as a conservative scenario that its market share will be taken over by competitors within two years after the Sunset date (SEA, p.47) and estimates that the economic loss from a societal perspective would be €1-5 million (value discounted to end of 2021 prices, using an annual discount factor of 4 %).

According to the applicant, the downstream users will have to introduce and validate new tests and methods should the continued use of the FISH tests offered by the applicant not be authorised. Additionally, the introduction of new tests will require the purchase of new equipment and training of personnel by the DU laboratories. At the request of SEAC, the applicant provided an estimation of the economic impacts to the downstream users to replace the FISH assays. The respective cost in terms of revenue losses due to downtime, replacement cost and training cost is estimated by the applicant to be €100-500 million (in 2021 prices, confidential range). Although no precise figure is given, the applicant concludes that the replacement cost alone amount to more than €10 million across all the DUs.

Furthermore, the manufacturers of targeted therapy drugs may also be impacted because their products rely on the use of the Companion Diagnostics. If the use of the substance is not authorised, the drug manufacturers may have to conduct clinical trials and submit new regulatory approvals for their drugs. The cost of clinical trials for these drugs can be as high as $33 million. Furthermore, patients will not have access to the drug during the revalidation period and the manufacturers will lose the corresponding revenue.

A refused authorisation will also increase the human health risks for patients whose specimens are currently tested with the applicant's FISH products. Over 400 000 tests are run annually using the applicant's FISH kits to diagnose, monitor and support treatment decisions on several types of cancer. In case of a refused authorisation, the applicant's customers will most likely not be able to substitute FISH with alternative methods without disruptions. Shortage of FISH test capacity could lead to delays in doctors' decisions, which may cause patients' conditions to worsen. Furthermore, particularly in the cases of Companion Diagnostics, it is likely that a less than optimal treatment will be selected for the patient if there is no access to FISH results. This could potentially result in a less effective therapy and more serious side effects.

On the other hand, the reduction in the manufacturing of FISH assay kits in the US plant will result in 5 to 50 employees losing their jobs at that location. The number of unemployed

workers in the EU is estimated to be in the range of 10-100 employees, 5 to 50 in the distribution centre in Wiesbaden, Germany, and the rest in the commercial offices in several EU member states. The total social cost of unemployment in the EU in case of a refused authorisation is expected to be €1-10 million.

Additionally, according to the applicant, the cease in the supply of their FISH assay kits to the EU will have a negative impact on competition. At present there are only five companies who offer this service in the EU and if the applicant leaves the market, the level of competition will be lower, which could have a negative impact for users of FISH kits that may face higher prices and fewer product options which may not suit their requirements.

Table 4: 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	More than €10 million for downstream users who currently perform the FISH tests and would have to switch equipment and train staff.
1.2 Avoided profit loss due to ceasing the use applied for	- The applicant expects €1-10 million losses in profits over 7 years but acknowledges that the actual producer surplus loss is likely to be in the range of €1-5 million and occurs over two years needed to replace and train staff on competitor equipment. - Downstream users and drug manufacturers that rely on Companion Diagnostic tests for their drugs will face profit losses (unquantified) resulting from the shortage of FISH tests while they are looking for an alternative method.
1.3 Avoided relocation or closure cost	n/a
1.4 Avoided residual value of capital	n/a
1.5 Avoided additional cost for transportation, quality testing, etc.	Manufacturers of targeted therapy drugs connected to Companion Diagnostic tests will face the cost of additional clinical trials and regulatory approval for alternative tests, and the loss of profits resulting from the lack of marketing of the targeted therapy drug in the period required to conduct the clinical trials.
Sum of benefits to the applicant(s) and / or their supply chain	- Avoided welfare cost of at least €11 million - Unquantified avoided loss of profits for downstream users and drug manufacturers - Avoided costs in clinical trials and regulatory approvals for drug manufacturers.
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[13]	€1-10 million
2.2 Foregone spill-over impact on surplus of alternative producers	n/a
2.3 Avoided consumer surplus loss (e.g. because of inferior quality, higher price, reduced quantity, etc.)	- More than 400 000 tests are run annually using the applicant's FISH kits to diagnose, monitor and support treatment decisions on several types of cancer. In case of a refused authorisation, the applicant's customers will most likely not be able to substitute FISH with alternative methods before the Sunset Date. - Shortage of FISH test capacity could lead to delays in doctors' decisions and consequently detrimental health outcomes. - Furthermore, particularly in the cases of Companion Diagnostics, it is likely that a less than optimal treatment will be selected for the patient if there is no access to FISH results. This could potentially result in a less effective therapy and more serious side effects. - Reduced competition (there are only 5 companies on the market at present) may also result in higher prices and fewer product options for downstream users.
2.4 Avoided other societal impacts (e.g. avoided CO_2 emissions or securing the production of drugs)	
Sum of impacts of continuation of the use applied for	- Social cost of unemployment of €1-10 million - Avoided delays in the diagnosis of cancer and prescription of less effective therapies for a number of patients (over 400 000 FISH tests are conducted annually) - Avoided higher prices and fewer product options for downstream users due to reduced competition
3. Aggregated socio-economic benefits (1+2)	- Total quantified welfare cost of at least €12 million - Unquantified avoided loss of profits for downstream users and drug manufacturers. - Avoided costs in clinical trials and regulatory approvals for drug manufacturers. - Avoided delays in the diagnosis of cancer and prescription of less effective therapies for a number of patients (over 400 000 FISH tests are conducted annually). - Avoided higher prices and fewer product options for downstream users due to reduced competition.

[13] Job losses to be accounted for only for the arithmetic mean period of unemployment in the concerned region/country as outlined in the SEAC paper on the valuation of job losses (See The social cost of unemployment and Valuing the social costs of job losses in applications for authorisation).

5.3. Combined assessment of impacts

The applicant concludes that if an authorisation is granted for the use, 12.5 kg/year will be released to the environment during the review period requested. During the same period (2021-2027), the Applicant is expected to lose profits of approximately €1-10 million. However, as acknowledged by the applicant, it is likely that some of these losses may be compensated through gains to competitors. The applicant estimates the overall producer surplus loss to be in the range of €1m to €5m, which would occur over a period of 2 years during which DUs would switch to competitor products. For the DUs, the non-availability of the applicant's FISH assays would result in costs for replacing equipment and training staff, which the applicant quantified to be at least €10m (corresponding to €10 000 to €100 000 per average DU affected).

Additionally, in case of a refused authorisation, it is expected that 5-50 employees will lose their job in the applicant's manufacturing plant outside of the EU and approximately 10-100 employees in EU facilities. The social cost of unemployment, if these EU employees are made redundant would be €1-10 million.

Taking the impacts together, SEAC finds that the monetized benefit of an authorisation amounts to at least €12 million and may well be larger than €20 million. Considering the minimum monetized benefit of authorisation and the maximum quantity of 4-tert-OPnEO released over 7 years, the benefit of authorisation is at least €137 000 per kg of 4-tert-OPnEO emitted.

The economic impacts for the applicant's customers have been monetised by the applicant at the request of SEAC and are estimated by the applicant to consist of €100-500 million (2021 € prices) in revenue losses due to downtime, replacement cost for switching equipment and training cost. Even in the best case, these costs correspond to resource implications in excess of €10 million, which was used as a lower bound estimate by SEAC for the quantitative comparison of impacts in Table 6.

SEAC stresses that possible impacts to patients' health were described qualitatively by the applicant but were not taken into account in the calculation of the costs of preventing the remaining releases of 4-tert-OPnEO. However, SEAC concurs with the applicant that these are important impacts as they relate to human health.

Table 5: Socio-economic benefits and risks of continued use

Socio-economic benefits of continued use		**Excess risks associated with continued use**	
Benefits	At least €12 million (profit loss of applicant for 2 years plus avoided investment of DUs into equipment and training plus unemployment cost)	Monetised excess risks to workers directly exposed in the use applied for	n/a
Quantified impacts of the continuation of the SVHC use applied for	n/a	Monetised excess risks to the general population and indirectly exposed workers	n/a
Additional qualitatively assessed	- Unquantified avoided loss of profits for	Additional qualitatively assessed	Emissions of the substance of

Socio-economic benefits of continued use		Excess risks associated with continued use	
impacts	downstream users and drug manufacturers. - Avoided costs in clinical trials and regulatory approvals for drug manufacturers. - Avoided delays in the diagnosis of cancer and prescription of less effective therapies for a number of patients (over 400 000 FISH tests are conducted annually). - Avoided higher prices and fewer product options for downstream users due to reduced competition.	risks	12.5 kg/year over the review period.
Summary of socio-economic benefits	- Quantified benefits of at least €12 million - Unquantified avoided loss of profits for downstream users and drug manufacturers. - Avoided costs in clinical trials and regulatory approvals for drug manufacturers. - Avoided delays in the diagnosis of cancer and prescription of less effective therapies for a number of patients (over 400 000 FISH tests are conducted annually). - Avoided higher prices and fewer product options for downstream users due to reduced competition.	**Summary of excess risk**	Emissions of the substance of 87.5 kg over the review period.

Table 6: Cost of non-use per kg

	Review period (7 years)
Total societal cost (€)	€12 million
Total emissions (kg)	87.5
Ratio (€/kg)	At least €137 000 per kg

Notes:

1. "Total cost" (of non-authorisation) = Benefit of authorisation
2. "Total emissions" (if authorisation is granted) = Estimated emissions to the environment, based on Table 2.
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 foresees the cease of supply of FISH assay kits containing 4-tert-OPnEO to their EU customers is justified, because of the lack of available alternatives to the applicant, the consequences of non-availability of these product to DUs, and the time and resources needed for substitution.

Over 400 000 tests are run annually using the Applicant's FISH tests in laboratories and clinics in the EU. The tests are used in oncological diagnosis of conditions such as chronic lymphocytic leukaemia (CLL) and non-small cell lung cancer and are critical components for targeted therapies. Some FISH assays kits such as the Vysis CLL for venetoclax, are the only companion diagnostics therapy that is approved and can be used with the biologic drug they are associated with.

SEAC notes that the assessment of benefits of continued use does not quantify the potentially severe impacts of not having available the FISH tests made by the applicant in the medium and long term. The applicant assumes that competitors could replace their products in two years' time but has no indication if these present or future products would not also contain 4-tert-OPnEO. Therefore, it is not clear to SEAC if alternative products would remain available in sufficient quantities in the EEA. If this was not the case, then the assessment of the applicant reflects only a small part of the social benefits of continued use.

The main cost element quantified by the applicant is the cost to downstream users in case of a non-authorisation. According to the applicant, laboratories could face a shortage of FISH tests for 9-12 months on average before they could introduce a replacement. The economic losses to downstream users are estimated to be in the range of €100-500 million (2021 € prices, range confidential). SEAC notes that the benefits include the purchase of replacement technology, the training of personnel and the loss of revenue for the laboratories as a result of switching to a competitor product and the downtime induced by such switches. SEAC notes revenues are not a suitable welfare impact but accepts the applicant's argumentation that they are not in the position to speculate about downstream users' profit margins. Moreover, the replacement cost is the major cost driver in the applicant's assessment. Under the most conservative assumptions these are in SEAC's view in excess of €10 million.

According to the applicant FISH is a versatile method suitable for a wide range of analytes and cannot be replaced by a single technique. The costs to replace FISH testing in the customer labs depends on the method that will be selected. While SEAC acknowledges that the laboratories may face additional costs for the introduction of new technology, it does not consider appropriate to use the revenue loss in the calculation. The applicant recognises the

uncertainty of the monetisation of the costs for downstream users and the lack of information regarding the profit margin of the laboratories. In fact, the monetisation of the costs for the downstream users was not included in the SEA analysis of the application but was submitted by the applicant at the request of SEAC. Nevertheless SEAC notes that even if the revenue loss is not considered in the monetisation of the costs, the costs for the downstream users on equipment would still be larger than €10 million.

The economic impacts for the applicant results from the profit losses expected to accrue to them if an authorisation for use of the substance is not granted. Consistent with the non-use scenario, these profit losses are calculated over the review period requested of 7 years. SEAC considers that changes in profits are a relevant measure of changes in producer surplus and appropriate to monetising the welfare implication of continued use. However, changes in profits made by the applicant do not necessarily reflect changes in economic surplus across the EU economy. In particular, the applicant argues that its direct competitors would take over the abandoned market shares in two years' time in the non-use scenario. As this would imply producer surplus gains for the competitors, these gains would likely compensate in the long run for the surplus losses made by the applicant. Therefore, SEAC does not consider it appropriate to use the profit loss incurred by the applicant over 7 years but notes that even if one considered only two years of profit loss—the time needed to switch to a competitor's system as argued by the applicant—the producer surplus loss from a refused authorisation would still be in the range of €1-5 million.

As for the occurrence of impacts, it is true that the applicant's owner is a US company but the profits of selling the FISH assay kits will accrue to their EU subsidiary and hence SEAC finds it acceptable to incorporate these profit losses into the calculations presented in Table 4 to Table 6.

SEAC considers that the most plausible non-use scenario would result in unemployment of some of the applicant's workers. The approach to monetise the impacts follows the SEAC methodology.[14] SEAC notes that this impact would present a significant welfare cost and can be considered a significant benefit of continued use.

SEAC's assessment obtains a value of €137 000 per kg of prevented emissions of 4-tert-OPnEO based on the most conservative elements from the applicant's non-confidential assessment (i.e. using minimum benefits).

SEAC takes note of the conclusion of RAC on the risks from the use applied for.

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.

[14] Dubourg, R. (2016) Valuing the social costs of job losses in applications for authorisation. Available at: https://echa.europa.eu/documents/10162/13555/unemployment_report_en.pdf/

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 did not provide any advice on the length of the review period.

6.2. Substitution and socio-economic considerations

The applicant requests a review period of 7 years for substitution of 4-tert-OPnEO in FISH assays.

SEAC considers that the substitution timelines proposed by the applicant are reasonable, especially when considering the regulatory review cycle times required by several countries.

The applicant follows a staged approach to rollout of approximately 400 updated products not using 4-tert-OPnEO. This staged approach requires the requested review period of 7 years for completion. SEAC notes that the applicant has already successfully substituted 4-tert-OPnEO in a product that was under development which underlines the credibility of the applicant's substitution effort.

Taking into account these points, SEAC recommends a **7-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

All the liquid and solid waste shall be collected for adequate treatment. The treatment shall minimise releases to environmental compartments as far as technically and practically possible. Release into the sewer system or to surface waters is not considered to constitute adequate treatment.

[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.

SEAC

Proposed additional conditions

None

7.2. Justification

There is no requirement in the applicant's ES for downstream users to collect solid and liquid waste for adequate treatment (e.g. for incineration).

Regarding solid waste, the applicant confirmed that the majority of its customers already have in place waste collection processes for solid laboratory waste and that the solid waste is disposed of as hazardous waste and incinerated. Nevertheless, the applicant was unable to conclude that collection and adequate treatment of solid waste occurred at all downstream users' sites, particularly related to contaminated single use containers, empty wash buffer bottles and clean up materials. The applicant did not indicate any technical difficulties, nor additional cost for all its customer to dispose of their solid waste as hazardous waste. RAC and SEAC concluded therefore that a condition to collect solid waste for adequate treatment is technically and practically possible, and would be economically feasible.

Regarding liquid waste, the applicant indicated that some of its downstream users are already collecting liquid waste for disposal via incineration. The applicant stated also that collecting liquid waste for incineration implies the installation of an additional capture system with associated costs for the DUs. In addition, the applicant stated that most of its DUs are SMEs (small and medium enterprises) that cannot absorb the cost associated with the implementation of additional collection systems, logistic and incineration of liquid waste for such a small quantity: 0.2 to 1 L per week of liquid waste.

Although collecting liquid waste for adequate treatment (e.g. incineration) might imply the installation of additional capture system and costs for downstream users, RAC and SEAC note that the collection of low volumes of liquid waste generated by downstream users (e.g. laboratories) should not present any significant technical challenge nor cost, taking into account that liquid wastes are to be removed manually from the FISH test equipment. Furthermore, the cost of handling liquid waste for incineration (estimated by the applicant at around €190 per liquid collection event up to 200 L) may result in an increase of operating cost of around €760 per year and laboratory (assuming four quarterly collections).

RAC and SEAC conclude therefore that a condition to collect liquid waste for adequate treatment is technically and practically possible, and would be economically feasible.

In addition RAC considers that these additional conditions will be temporary, until 4-tert-OPnEO is replaced by a suitable alternative, and that these measures might already be in place at some downstream user sites as indicated by the applicant.

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

Not applicable.

9. Recommendations for the review report

Were recommendations for the review report made?

☒ Yes

☐ No

9.1. Description

In case a review report is submitted, the applicant shall report on a representative survey of their downstream users about the collection and treatment methods that are applied (e.g. incineration) for the liquid and solid waste following from the requirement to collect all liquid and solid waste for adequate treatment.

9.2. Justifications

In line with the proposed additional condition for the authorisation (see Section 7), a representative downstream user survey will allow RAC to evaluate the remaining releases to environmental compartments which in part depends on the effectiveness of the liquid and solid waste treatment method.

10. Comments on the draft final opinion

Did the applicant provide comments on the draft final opinion?

☐ Yes

☒ No

[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.

10.1. 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

Not applicable – the applicant did not comment.

10.3. Reasons for not amending the opinion

Not applicable – the applicant did not comment.