Committee for Risk Assessment (RAC)

Committee for Socio-economic Analysis (SEAC)

Final Opinion

on an Application for Authorisation for

Trichloroethylene use:

Use of trichloroethylene as a processing aid in the biotransformation of starch to obtain betacyclodextrin

ECHA/RAC/SEAC: Opinion N° AFA-O-0000006013-87-02/F

Consolidated version

Date: 21 April 2015

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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 an application for authorisation for:

Chemical name(s): **Trichloroethylene**
EC No.: **201-167-4**
CAS No.: **79-01-6**

for the following use:

Use of trichloroethylene as a processing aid in the biotransformation of starch to obtain betacyclodextrin.

Intrinsic property referred to in Annex XIV:

Article 57 (a) of the REACH Regulation.

Applicant:

ROQUETTE Frères

Reference number:

11-2120060132-73-0000

Rapporteur, appointed by the RAC: Christine BJØRGE
Co-rapporteur, appointed by the RAC: Normunds KADIĶIS

Rapporteur, appointed by the SEAC: Simon COGEN
Co-rapporteur, appointed by the SEAC: Karmen KRAJNC

This document compiles the opinions adopted by RAC and SEAC.

PROCESS FOR ADOPTION OF THE OPINIONS

On 29 August 2014 ROQUETTE Frères submitted an application for authorisation including information as stipulated in Articles 62(4) and 62(5) of the REACH Regulation. On **29 October 2014** ECHA received the required fee in accordance with Fee Regulation (EC) No 340/2008. The broad information on uses of the application was made publicly available at http://echa.europa.eu/addressing-chemicals-of-concern/authorisation/applications-for-authorisation on **12 November 2014**. Interested parties were invited to submit comments and contributions by **07 January 2015**.

No comments were received from interested parties during the public consultation in accordance with Article 64(2).

The draft opinions of RAC and SEAC take into account the responses of the applicant to the requests that the SEAC made according to Article 64(3) on additional information on possible alternative substances or technologies.

The draft opinions of RAC and SEAC were sent to the applicant on **2 April 2015**.

On **17 April 2015** the applicant informed ECHA that they did not wish to comment on the opinions. The draft opinions of RAC and SEAC were therefore considered as final on **21 April 2015**.

ADOPTION OF THE OPINION OF RAC

The draft opinion of RAC

The draft opinion of RAC, which assesses the risk to human health and/or the environment arising from the use of the substance – including the appropriateness and effectiveness of the risk management measures as described in the application and, if relevant, an assessment of the risks arising from possible alternatives – was reached in accordance with Article 64(4)(a) of the REACH Regulation on **12 March 2015**.

The draft opinion of RAC was agreed by consensus

The opinion of RAC

Based on the aforementioned draft opinion and in the absence of comments from the applicant, the opinion of RAC was adopted as final on **21 April 2015**.

ADOPTION OF THE OPINION OF SEAC

The draft opinion of SEAC

The draft opinion of SEAC, which assesses the socio-economic factors and the availability, suitability and technical and economic feasibility of alternatives associated with the use of the substance as described in the application was reached in accordance with Article 64(4)(b) of the REACH Regulation on **13 March 2015**.

The draft opinion of SEAC was agreed by consensus.

The opinion of SEAC

Based on the aforementioned draft opinion and in the absence of comments from the applicant, the opinion of SEAC was adopted as final on **21 April 2015**.

THE OPINION OF RAC

The application included the necessary information specified in Article 62 of the REACH Regulation that is relevant to the Committee's remit.

RAC has formulated its opinion on the risks arising from the use applied for and the appropriateness and effectiveness of the described risk management measures and on the assessment of the risks related to the alternatives as documented in the application and on information submitted by interested third parties as well as other available information.

RAC confirmed that it is not possible to determine a DNEL for the carcinogenicity properties of the substance in accordance with Annex I of the REACH Regulation.

RAC confirmed that there appear not to be any suitable alternatives that further reduce the risk.

RAC confirmed that the operational conditions and risk management measures in the application appear to limit the risk, provided that the risk management measures and operational conditions as described in the application and the suggested conditions and monitoring arrangements are adhered to.

THE OPINION OF SEAC

The application included the necessary information specified in Article 62 of the REACH Regulation that is relevant to the Committee's remit.

SEAC has formulated its opinion on the socio-economic factors and the availability, suitability and technical and economic feasibility of alternatives associated with the use of the substance as documented in the application and on information submitted by interested third parties as well as other available information.

SEAC took note of RAC's confirmation that it is not possible to determine a DNEL for the carcinogenicity properties of the substance in accordance with Annex I of the REACH Regulation.

SEAC confirmed that there appear not to be suitable alternatives in terms of their technical and economic feasibility for the applicant

SEAC considered that the applicant's assessment of (a) the potential socioeconomic benefits of the use, (b) the potential adverse effects to human health or the environment of use and (c) the assessment used to compare the two is based on acceptable socio-economic analysis. Therefore, SEAC did not raise any reservations that would change the validity of the applicant's conclusion that overall benefits of the use outweigh the risk to human health or the environment, whilst taking account of any uncertainties in the assessment provided that the suggested conditions and monitoring arrangements are adhered to.

SUGGESTED CONDITIONS AND MONITORING ARRANGEMENTS

Conditions

Monitoring arrangements

The following monitoring arrangements are recommended in case the authorisation is granted:

The applicant must implement regular campaigns of occupational exposure measurements (sampling at least annually) relating to the use of TCE described in this application. These monitoring campaigns must be based on relevant standard methodologies or protocols and comprise both personal inhalation exposure sampling and biomonitoring (measurement of the TCE metabolite TCA in urine), be representative of the range of tasks undertaken where exposure to TCE is possible and of the total number of workers that are potentially exposed (i.e. the campaign shall include process and maintenance workers).

The results of the monitoring must be included in any subsequent authorisation review report submitted.

REVIEW

Taking into account the information provided in the analysis of alternatives prepared by the applicant the duration of the review period for the use is recommended to be **12 years**.

JUSTIFICATIONS

The justifications for the opinion are as follows:

1. The substance was included in Annex XIV due to the following property/properties:

- ☒ 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):

2. Is the substance a threshold substance?

- ☐ YES
- ☒ NO

Justification:

Trichloroethylene (TCE) has a harmonised classification with Carc. 1B; H350 and Muta. 2; H341 according to CLP. Based on studies which show its genotoxic potential, the Risk Assessment Committee (RAC) has concluded that trichloroethylene should be considered as a non-threshold carcinogen with respect to risk characterisation (reference to the studies examined are included in the RAC document RAC/28/2014/07 Rev. 2 Final).

3. Hazard assessment. Are appropriate reference values used?

Justification:

RAC has established a reference dose response relationship for kidney cancer following exposure to trichloroethylene (RAC 28/2014/07 Rev. 2 Final). Based on epidemiological data (cited in the RAC document) an increased risk of kidney cancer occurring with cytotoxicity was found following relatively high occupational exposure including very high peak exposure. Thus a linear dose-response relationship would overestimate the risk at low exposure levels where no cytotoxicity would occur. Therefore a sub-linear approach with a break point at 6 ppm (33 mg/m^3) was considered by RAC to be the most scientifically justified approach. RAC has not derived a DMEL value for trichloroethylene.

In the socio-economic analysis (SEA) the remaining human health risks are evaluated based on the dose-response relationship adopted by RAC.

4. Exposure assessment. To what extent is the exposure from the use described?

Please describe:

Introduction:

At the Roquette facilities trichloroethylene (TCE) is entirely handled outdoors in batch processes, during 2 campaigns of 3 month each per year. The applicant presents one exposure scenario in the Chemical Safety Report (CSR) that describes the use: *Use at industrial site – Roquette site (Use of trichloroethylene as a processing aid in the biotransformation of starch to obtain betacyclodextrin)*.

The Exposure scenario (ES) consists of an environmental contributing scenario (ECS) and five worker contributing scenarios (WCS). Additional information from the applicant received upon request clarified that WCS5 is not longer relevant. The applicant uses 3 tonnes TCE/year. TCE is delivered in SAFETAINER. The environmental release and the exposure to Man via the environment is addressed. The excess kidney cancer risk for workers is in the order of 10^{-4} and for Man via the environment in the order of 10^{-8} to 10^{-12}.

Exposure scenarios:

Exposure scenario 1: Use at industrial site – Roquette site - Use of trichloroethylene as a processing aid in the biotransformation of starch to obtain betacyclodextrin

The applicant described the following steps for the exposure scenario in the CSR (ES1):
ECS[1]1: Use at industrial site – Roquette
WCS[2]1: Storage (PROC 1)
WCS2: Transfer of substance using dedicated facilities (PROC 8b)
WCS3: Use in batch processes with opportunity for exposure (PROC 4)
WCS4: Maintenance and cleaning of the equipment (PROC 8a)
WCS5: Use as laboratory agent (PROC 15), however not longer relevant as this activity has ceased.

Information on worker exposure: The amount of substance used, the duration and frequency of tasks, the number of workers exposed, the measured and modelled exposures and the use of RPE/PPE in the five worker contributing scenarios are included in Annex I to the opinion. The exposure values applied to estimate the number of kidney cancer cases is written in bold text in the Annex. The individual tasks are described in sufficient details by the applicant to allow an assessment of the worker exposure.

Additional information was submitted, by the applicant, upon request from RAC regarding the involvement of the same workers in multiple tasks covered by more than one WCS, as well as additional information regarding the measured exposure data in WCS 3; moreover, updated information regarding WCS5 was given.

[1]'ECS' denotes environmental contributing scenario
[2] 'WCS' denotes working contributing scenario

Methodology used by the applicant:

Worker exposure:
Personal air measurements with carbon tube and gas chromatography (ISO16200-1) are available for WCS3 from 2014. Three measurements each of 5h duration are available. However, these were taken from an overall contribution of five workers divided over two shifts where the new operators continued to use the same carbon tube as the previous operators.

Stationary measurements with carbon tube and gas chromatography (ISO16200-1) were available from two locations, one from the top of a reactor and one from the TCE treatment area.

Internal inspection (referred to as "check tour" in the documentation provided by the applicant) air measurements using Dräger tubes and air pumps before 2014 were available for WCS 1, 2, 3 and 4 (maximum value of historical data).

Modelled data have also been submitted by the applicant. For inhalation and dermal exposure. ECETOC TRA v3 was used to estimate the exposure for the five WCS. No biological monitoring data of the employees at Roquette site is carried out to date according to the applicant.

Measured data normally gives more realistic information regarding the workplace exposure to TCE compared to modelled data that are considered to overestimate the exposure. For WCS3 the ECETOC TRA v3 was used for inhalation exposure. Modelled data from WCS3 were significantly higher than the measured exposure. However, the measured data was from three measurements each of 5h duration. Furthermore, the measured data was taken from an overall contribution of five workers divided over two shifts where the new operators continued to use the same carbon tube as the previous operators. Consequently, there are uncertainties related to the measured data and should therefore be considered to be indication of exposure to TCE. So, the preference should be given to the modelled data, however, taking into account that these values likely represent an overestimation of worker exposure to TCE from WCS3.

For the calculation of excess kidney cancer risk in the CSR, modelled data were used for inhalation and dermal exposure for all five WCS. In the exposure assessment the use of PPE including gloves (assumed to reduce exposure by 90%, conforming to EN374) is described for all the five WCS. Respiratory protection equipment (RPE) is included for WCS2 and WCS4 (3M, ref. 4277 type FFABE1P3RD, assumed to reduce the exposure by 90%, APF 10). The use of gloves was assumed to reduce the exposure by 90% and RPE was assumed by the applicant to reduce the exposure by 90% (APF 10). In the dermal estimate the use of PPE is taken into consideration in the modelling.

Exposure of man via the environment:
The exposure of Man via the environment (inhalation and oral) was estimated with EUSES 2.1.2.

Exposure estimated by applicant
At the Roquette facilities TCE is handled outdoors in batch processes, during 2 campaigns of 3 month each year. Twelve operators are involved in these campaigns, usually 2 per 8-hour shift.

Inhalation exposure for workers:
WCS1 (one operator):
The applicant used modelled data for the daily TCE exposure of 0.008 mg/m^3 with a duration of < 1 hour, (and a frequency of 10 operations per year) The measured data obtained with Dräger tubes during inspection tours before 2014 were < 5 mg/m^3.

WCS2 (two operators):
The applicant used modelled data for the daily TCE exposure of 1.916 mg/m^3 with a duration of < 1 hour, (2 operations/year)

WCS3 (six operators):
The applicant used recent measured data for the daily TCE exposure of 0.3 mg/m^3 (reported by the applicant as three measurements indicating < 0.2, < 0.4 and < 0.21 mg/m^3). However, these were taken from an overall contribution of five workers divided over two shifts where the new operators continued to use the same carbon tube as the previous operators. Furthermore, the measured data was also taken outdoors where changes in wind direction or the route taken to go from one location to another location may affect the measured exposure level. RAC therefore consider that there are significant uncertainties related to the measured data and are of the opinion that the modelled data of 15.33 mg/m^3 should be used for WCS3. However, RAC are aware that the modelled data represent an overestimation of the worker exposure. The measured data obtained with Dräger tubes before 2014 were < 5 mg/m^3.

WCS4 (two operators):
The applicant used modelled data for the daily TCE exposure of 3.832 mg/m^3 with duration of < 2 hour. The measured data performed with Dräger tubes before 2014 were < 25 mg/m^3.

WCS5 (one operator):
The applicant used modelled data for the daily TCE exposure of 0.328 mg/m^3 with duration of < 1 hour. However, the applicant informed, upon request, that the practice is changed in 2015 and that the CSR reflects what Roquette did in the past. Up to the end of 2014 the sample was taken at the end of the reaction from medium containing TCE and taken to the laboratory for analysis. Current practise is to take an "in line" measurement to remove the risk of exposure to TCE, therefore the applicant considers that there is no exposure to TCE from WCS5.

Dermal exposure for workers:
WCS1 (one operator):
The applicant used modelled data for the daily TCE exposure of 6.8 x 10^{-4} mg/kg bw/day.

WCS2 (two operators):
The applicant used modelled data for the daily TCE exposure of 0.274 mg/kg bw/day.

WCS3 (six operators):
The applicant used modelled data for the daily TCE exposure of 0.137 mg/kg bw/day.

WCS4 (two operators):
The applicant used modelled data for the daily TCE exposure of 0.274 mg/kg bw/day.

WCS5 (one operator):
The applicant used modelled data for the daily TCE exposure of 0.007 mg/kg bw/day. However, today there is no dermal exposure to TCE from this WCS, see more information above.

Combined exposure:
The applicant informed upon request that the operations are managed with 6 teams of 2 operators. Their work includes routine operations (WCS3) as well as one-time operations including WCS 1, 2 and 4. Combined exposure for inhalation and dermal exposure from WCS 1, 2 3 and 4 are therefore estimated, see table 1 below. WCS5 is not included in the combined exposure given that, as from 2015, no exposure is likely to occur from this WCS, according to the applicant, as an "in line" measurement is used to take a sample for analysis.

Table 1: Combined exposure from WCS 1 to WCS 4 reported by the applicant

WCS	**Inhalation exposure CSR mg/m^3**	**Inhalation exposure Dräger tubes mg/m^3*****	**Dermal exposure CSR mg/kg bw/day**
WCS1*	0.008	< 5	6.8 x 10^{-4}
WCS2*	1.916	< 5	0.274
WCS3* WCS3**	15.33 0.3	< 5	0.137
WCS4*	3.832	< 25	0.274
Combined exposure (WCS1-WCS4)	21.086* 6.056**	< 40	0.686

*Modelled data
**Measured data WCS3
***Maximum of historical data before 2014

Indirect exposure of Man via the environment

The oral exposure from food consumption and drinking water and via inhalation was estimated using EUSES 2.1.2. Air monitoring data are also available from Roquette site showing levels of 0.17 mg/m^3 as a maximum, however the applicant used EUSES 2.1.2 for the estimation of local and regional exposure to TCE since the measured value at 0.17 mg/m^3 was sampled very close to the TCE storage. The local oral exposure was estimated to be 3.438 x 10^{-6} mg/kg bw/day and the local inhalation exposure 0.001 mg/m^3. The regional oral exposure was estimated to be 6.37 x 10^{-11} mg/kg bw/day and regional inhalation exposure 8.517x10^{-8} mg/m^3.

5. If considered a threshold substance, has adequate control been demonstrated?

☐ YES

☐ NO

☒ NOT RELEVANT, NON THRESHOLD SUBSTANCE

Justification:

RAC has concluded that trichloroethylene should be considered as a non-threshold carcinogen with respect to risk characterisation.

6. If adequate control is not demonstrated, are the operational conditions and risk management measures described in the application appropriate and effective in limiting the risk?

☒ YES

☐ NO

Justification:

The calculation of the remaining human health risk is based on the dose-response relationship published by RAC (RAC 28/2014/07 Rev.2 Final) and the estimated worker exposure levels. The overall risk is determined for workers at the Roquette site resulting from exposure to TCE by inhalation and dermal contact. The risk for the general population due to oral intake of TCE from food consumption and drinking water or inhalation exposure to TCE near the Roquette site as well as risk from regional exposure was not determined in the CSR but provided by the applicant upon request.

Workers:

Kidney cancer in workers due to inhalation and dermal exposure to TCE is considered to be the critical effect for risk assessment. Based on the sub-linear dose-response relationship established by RAC the excess lifetime kidney cancer mortality risk for workers has a breakpoint at 33 mg/m^3 (6ppm) with an excess kidney cancer risk in EU workers at 4.0 x 10^{-4}.

For inhalation exposure the excess risk at 33 mg/m^3 and above is **1.3 x 10^{-4} per mg TCE/m^3 – 0.0039**, and below 33 mg/m^3 the excess risk is **1.2 x 10^{-5} per**

mg TCE/m^3 (based on 8h exposure 5 days/week during 40 years).

For dermal exposure the breakpoint for the sub-linear dose-response curve is 4.72 mg/kg bw/day with an excess kidney cancer risk in EU workers at 4x10^{-4}.

At 4.72 mg/kg bw/day and above the excess risk is **9.09 x 10^{-4} per mg TCE/kg bw/day – 0.0039** and below 4.72 mg/kg bw/day **8.4 x 10^{-5} per mg TCE/kg bw/day** (based on 8h exposure 5 days/week during 40 years).

WCS 1 Storage:

Based on the exposure data described above and taking into account the frequency and duration of the process (2 times per year for 3 months) the excess kidney cancer risk via inhalation exposure is 0.008 mg/m^3 x 1.2 x 10^{-5} per mg TCE/m^3 = 9.6 x 10^{-8}. To account for 6 month of TCE exposure the risk was multiplied with a factor of 0.5 resulting in an excess kidney cancer risk of 4.8 x 10^{-8}. Via dermal exposure the excess kidney cancer risk for daily activities is 6.8 x 10^{-4} mg/kg bw/day x 8.4 x 10^{-5} per mg TCE/kg bw/day = 5.712 x 10^{-8}. Multiplied with a factor of 0.5 due to the frequency and duration of the process the excess kidney cancer risk is 2.856 x 10^{-8}. The excess kidney cancer risk for combined (inhalation and dermal) exposure for WCS1 is calculated to be **7.656 x 10^{-8}**.

WCS 2 Transfer of substance using dedicated facilities:

Based on the exposure data described above and taking into account the frequency and duration of the process (2 times per year for 3 months) the excess kidney cancer risk via inhalation exposure is 1.961 mg/m^3 x 1.2 x 10^{-5} per mg TCE/m^3 = 2.353 x 10^{-5}. To account for 6 month of TCE exposure the risk was multiplied with a factor of 0.5 resulting in an excess kidney cancer risk of 1.176 x 10^{-5}. Via dermal exposure the excess kidney cancer risk for daily activities is 0.274 mg/kg bw/day x 8.4 x 10^{-5} per mg TCE/kg bw/day = 2.3 x 10^{-5}. Multiplied with a factor of 0.5 due to the frequency and duration of the process the excess kidney cancer risk is 1.15 x 10^{-5}. The excess kidney cancer risk for combined (inhalation and dermal) exposure for WCS2 is calculated to be **2.326 x 10^{-5}**.

WCS 3 Use in batch processes with opportunity for exposure:

Based on the exposure data described above and taking into account the frequency and duration of the process (2 times per year for 3 months) the excess kidney cancer risk via inhalation exposure is 15.33 mg/m^3 x 1.2 x 10^{-5} per mg TCE/m^3 = 1.84 x 10^{-4}. To account for 6 month of TCE exposure the risk was multiplied with a factor of 0.5 resulting in an excess kidney cancer risk of 9.2 x 10^{-5}. Via dermal exposure the excess kidney cancer risk for daily activities is 0.137 mg/kg bw/day x 8.4 x 10^{-5} per mg TCE/kg bw/day = 1.16 x 10^{-5}. Multiplied with a factor of 0.5 due to the frequency and duration of the process the excess kidney cancer risk is 5.76 x 10^{-6}. The excess kidney cancer risk for combined (inhalation and dermal) exposure for WCS3 is calculated to be **9.78 x 10^{-5}**.

WCS 4 Maintenance and cleaning of the equipment:

Based on the exposure data described above and taking into account the frequency and duration of the process (2 times per year for 3 months) the excess kidney cancer risk via inhalation exposure is 3.832 mg/m^3 x 1.2 x 10^{-5} per mg TCE/m^3 = 4.6 x 10^{-5}. To account for 6 month of TCE exposure the risk was multiplied with a factor of 0.5 resulting in an excess kidney cancer risk of 2.3 x

10^{-5}. Via dermal exposure the excess kidney cancer risk for daily activities is 0.274 mg/kg bw/day x 8.4 x 10^{-5} per mg TCE/kg bw/day = 2.3 x 10^{-5}. Multiplied with a factor of 0.5 due to the frequency and duration of the process the excess kidney cancer risk is 1.15 x 10^{-5}. The excess kidney cancer risk for combined (inhalation and dermal) exposure for WCS4 is calculated to be **3.45 x 10^{-5}**.

WCS 5 Use as laboratory agent:

Based on the exposure data described above and taking into account the frequency and duration of the process (2 times per year for 3 months) the excess kidney cancer risk via inhalation exposure is 0.328 mg/m^3 x 1.2 x 10^{-5} per mg TCE/m^3 = 3.94 x 10^{-6}. To account for 6 month of TCE exposure the risk was multiplied with a factor of 0.5 resulting in an excess kidney cancer risk of 1.97 x 10^{-6}. Via dermal exposure the excess kidney cancer risk for daily activities is 0.007 mg/kg bw/day x 8.4 x 10^{-5} per mg TCE/kg bw/day = 5.9 x 10^{-7}. Multiplied with a factor of 0.5 due to the frequency and duration of the process the excess kidney cancer risk is 2.9 x 10^{-7}. The excess kidney cancer risk for combined (inhalation and dermal) exposure for WCS5 is calculated to be **2.26 x 10^{-6}**. However, as informed by the applicant (see section 4) this WCS is not taken into account in the application for authorisation.

Combined risk following exposure to WCS1 to WCS4:

In table 3 below the combined risk from dermal and inhalation exposure to TCE for workers doing daily activities including WCS1, 2, 3 and WCS 4. As regards the inclusion of WCS 5 in the combined exposure the applicant informed upon request that WCS5 is no longer relevant at Roquette site due to technical changes in 2015.

Table 2: Combined risk from inhalation and dermal exposure from WCS 1, 2, 3 and 4.

	Inhalation exposure CSR mg/m^3	**Dermal exposure CSR mg/kg bw/day**
Combined exposure	21.08	0.686
Combined risk	1.27 x 10^{-4}	2.9 x 10^{-5}

This results in an overall combined risk of **1.56 x 10^{-4}** for dermal and inhalation exposure.

In the CSR, the applicant described worker exposure as controlled and minimized. All workers at the Roquette site receive a safety introduction concerning the risk of TCE. The use of PPE and appropriate hygiene measures is defined in a procedure for each specific task. In the working area, operators wear basic PPE (overall, helmet, safety glasses, gloves and safety shoes). During tasks where significant exposure to TCE may be expected e.g. in case of leakage or

maintenance operations, the operators wear half-face masks and chemical suits. To protect against dermal exposure to TCE, nitrile gloves are used.

Maintenance is done > 1/month during an inspection tour after cleaning and checking for the presence of TCE with a DRAGER quick test.

The RMMs (risk managements measures) described by the applicant are considered to be appropriate and adequate to limit the exposure since TCE is only used in closed systems, under slight suction through air treatment with > 99.9% efficiency, and all the TCE equipment is located outside. The use of SAFETAINER prevents TCE leakage during transfer/pumping into the storage tank).

Indirect exposure to Man via the environment, not included in SEA

Kidney cancers following indirect exposure to Man via the environment due to inhalation and oral exposure to TCE are considered to be the effect of interest for risk assessment. Based on the sub-linear dose response relationship established by RAC the excess lifetime kidney cancer mortality risk for the general population has a breakpoint at 6.2 mg/m^3 with an excess kidney cancer risk in the general population at 4.0 x 10-4. For inhalation exposure the excess risk at 6.2 mg/m^3 and above is **6.9 x 10^{-4} per mg TCE/m^3 – 0.0039**, and below 6.2 mg/m^3 the excess risk is **6.4 x 10^{-5} per mg TCE/m^3** (based on 70 years of exposure).

For oral exposure the breakpoint for the sub-linear dose-response curve is 0.92 mg/kg bw/day with an excess kidney cancer risk in the general population at 4x10^{-4}. At 0.92 mg/kg bw/day and above the excess risk is **4.66 x 10^{-3} per mg TCE/kg bw/day – 0.0039** and below 0.92 mg/kg bw/day **4.32 x 10^{-4} per mg TCE/kg bw/day** (based on 70 years of exposure).

The excess kidney cancer risk for Man exposed via the environment was based on the local and regional exposure to TCE described above and calculated for combined exposure (oral and inhalation), see table 4 below. It can be concluded that the calculated excess kidney cancer risk for Man exposed via the environment is negligible. The calculated excess kidney cancer risk is far below the breakpoint determined for the general population in the RAC reference document (bearing in mind that this is not a threshold) and the measures taken within the Roquette site shows appropriate limitation of emission of TCE to the general population.

Table 3-: The excess kidney cancer risk from indirect exposure via the environment

Exposure	Inhalation	Oral	Combined risk
Local	6.4 x 10^{-8}	1.48 x 10^{-9}	6.55 x 10^{-8}
Regional	5.45 x 10^{-12}	2.75 x 10^{-14}	5.48 x 10^{-12}

In conclusion, RAC considers that the risk management measures and operational conditions as described in the application are appropriate and effective in limiting the risk to workers and the general population.

7. Justification of the suitability and availability of alternatives

7.1 To what extent is the technical and economic feasibility of alternatives described and compared with the Annex XIV substance?

Introduction

In the process presented in the application liquefied starch reacts with specific enzymes producing a hydrolysate solution, which contains betacyclodextrin (BCD). The hydrolysation step is then followed by the addition of activator trichloroethylene (TCE) - to precipitate the BCD, making it possible to separate the BCD from the hydrolysed starch. TCE is then stripped to obtain pure BCD. The applicant also uses the BCD further for the manufacturing of Hydroxypropyl-betacyclodextrin (HPBCD). HPBCD is a molecule with higher added value than BCD as it is the most frequently used cyclodextrin in pharmaceuticals, where it is the leading excipient used in patents and new pharmaceutical applications. The applicant currently uses 2 tonnes of TCE per year, but is planning to increase this volume to 3 tonnes in the next years, due to expected higher demand. Production runs for not more than 6 months (24/7) per year.

The choice of activator in the biotransformation of starch to obtain BCD is related directly to the enzymes used for hydrolysation. With the enzymes used by the applicant, TCE achieves 75 % complexation (i.e. yield), representing the benchmark "efficiency" of the reaction in order to compare it to alternatives.

TCE has also almost 100% stripping ability, which results in very pure BCD. This is of paramount importance, especially in the case of pharmaceutical use, one of the key sectors of customers of the applicant (90 % of its customers are in this sector).

The applicant has presented several alternatives (which were tested within the applicant's installation from 2003 onward). When assessing the alternatives the applicant took into account the following criteria:

- Compatibility with the enzymatic reaction process;
- Efficiency of the reaction compared to the TCE reaction;
- Ability to strip the solvent from the process and re-use it;
- Requirements on solvent residues for food and pharmaceutical products (Directive 2008/84 on food additives, European Pharmacopoeia);
- Flammability of the solvent and consequences for the applicant’s installation.

The applicant considered the following alternatives:

A. Gas chromatography (Solvent free)

This process uses UV light to synthesize BCD from starch and is suitable only for volumes below 1 tonne, which is far too little for the applicant. The reaction efficiency with gas chromatography is only 20 %.

The efficiency and the yield of the process would make it not suitable for industrial application; the applicant is unaware of method that would allow process to be scaled up.

In addition to this, the applicant would have to design a completely new installation as well. Such potential costs were not quantified, due to the fact that this alternative is technically not feasible.

Other criteria (stripping ability, flammability issue, and rules on solvent residues for food and pharmaceutical products) are not relevant for this alternative and were not touched upon by applicant.

The combination of the factors above would make this option not technically and economically feasible.

SEAC agrees that this alternative is technically and economically not feasible.

B. Toluene

Toluene is the most commonly used solvent for BCD's globally. Toluene has been the subject of repeated studies by the applicant.

The reaction efficiency with toluene is only 55 %. Besides this, the toluene has a poorer stripping ability; it takes longer to strip the toluene from the process resulting in a slower production process and causes additional cost (which were not quantified by the applicant).
Toluene is classified as highly flammable (H225) and would require either a change to the license(s) for the Lestrem site by the French authorities or (more likely) the physical relocation to another site to comply with ATEX Directive 94/9/EC (concerning equipment and protective systems intended for use in potentially explosive atmospheres).

The current location and reactor vats cannot be used with toluene, because they are too close to other installations and do not have the ATEX required perimeter of protection. There is sufficient space at the Lestrem site to build new installation, however the applicant would require a new permit for the additional amount of flammable liquid at their site (the applicant has a permit for 10 tonnes and would require a new permit for 12 tonnes).

According to the applicant, to obtain a permit to control potentially explosive atmospheres would be uncertain and extremely costly (if granted) as the village of Lestrem is near the plant site. In this case, the solution would be only in relocation to another site. Cost of building a new installation would be in the

range 10-100 M €.

Toluene is permitted as a residue for both food and pharmaceutical applications even in higher concentrations (800 times) than for TCE. However, as the residue of toluene is currently not declared on the applicant's medicine authorisations, a review of their dossier according to the pharmaceutical regulation would be required. Applicant quantified the total cost of fees to pharmaceutical companies at around 3 M €.

Toluene is available in sufficient quantities.

SEAC agrees that this alternative is technically and economically not feasible.

C. Perchloroethylene (PERC)

Reaction efficiency with PERC is 37.5 %. Therefore, the process must run twice as long compared to TCE to achieve the same result, which would have severe financial consequences, the cost in labour alone exceeds 1 M €/year. The applicant regards further process refinements to increase the efficiency of the process as not possible.

The applicant did not test the stripping ability, but believes that the higher solubility may lengthen the process even more.

PERC is not flammable.

PERC is not a permitted residue in pharmaceutical excipients or in food additives, which makes PERC inappropriate for the applicant's main customers.

PERC is available in sufficient quantities.

SEAC agrees that this alternative is technically and economically not feasible.

D. Dichloromethane (DCM)

Reaction efficiency with DCM is 15 %, which means a separate installation committed to just manufacturing BCD would need to be built because the current equipment is not sufficient to maintain the desired production level. Additional costs in labour would also be huge.

The applicant did not test the stripping ability.

DCM is not flammable.

Although DCM is available in sufficient quantities and it is a permitted residue in the pharmaceutical market, there are no medicine authorisations (and uses) known to the applicant for the excipient market (where the applicant has the strongest foothold). Dichloromethane is not a permitted residue in BCD according to the food additive regulation. Furthermore, although DCM is a permitted pharmaceutical residue, currently, there is no excipient market for HPBCD with DCM residue. This means that the production of the highly valuable HPBCD would cease, leading to severe financial losses. **SEAC agrees that this alternative is**

technically and economically not feasible.

E. Cyclohexane

Reaction efficiency with cyclohexane is 37,5% , meaning that the process must run twice as long, which would have severe financial consequences, the cost in labour alone exceeds 1 M €/year.

Applicant did not test the stripping ability.

The applicant referred to "issues of residues in both food and pharmaceuticals are being unresolved", but did not state more on this issue.

Cyclohexane is classified as extremely flammable (H225) because of the very low flashpoint (-20 °C), which means that the substance would be unsafe to use in a hot reaction like the BCD complexation.

The applicant did not elaborate further on economic feasibility, since it is clear that cyclohexane is technically not feasible.

Cyclohexane is available in sufficient quantities.

SEAC agrees that this alternative is technically and economically not feasible.

F. Isopropanol

Reaction efficiency with isopropanol is 20% (which means a separate installation committed to just manufacturing the BCD would have to be built because the current equipment would not be sufficient to maintain the desired production level.

Applicant did not test the striping ability.

The applicant did not elaborate further on economic feasibility, since it is clear that cyclohexane is technically not feasible.

Isopropanol is classified as extremely flammable (H225) because of the low flashpoint, which means that the substance would be unsafe to use in a hot reaction like the BCD complexation.

The applicant did not refer to the rules on solvent residues for food and pharmaceutical products.

Isopropanol is available in sufficient quantities.

SEAC agrees that this alternative is technically and economically not feasible.

SEAC does not consider any of the alternatives analysed to be technically and economically feasible.

7.2 Are the alternatives technically and economically feasible?

☐ YES

☒ NO

Justification:
The applicant considered six different alternative solvents.
SEAC considers that there is sufficient information in the application to conclude that no technically feasible alternatives exist for this use.

All alternative solvents would reduce the efficiency, resulting in additional costs connected to work force. In some cases current installation will not suffice, and new installation would need to be built.

Switching to any of the above described alternatives would have significant financial consequences: the technically most feasible alternative (toluene) would (due to its flammability) require building a new installation, at a cost of 10-100 M € (which is in the range of applicant's yearly turnover).
In the case of using a new solvent, notification of variations in accordance with pharmaceutical and/or food legislation will be needed, and could result in additional costs of 3 M €, with the possibility of losing some existing customers.

Based on its scrutiny of the Analysis of Alternatives, SEAC concurs with the assessment made by the applicant, which states that no technically and economically feasible alternatives will be available at the sunset date.

7.3 To what extent are the risks of alternatives described and compared with the Annex XIV substance?

Description:

Six potential alternatives are described, five alternative substances and one alternative technique. The applicant also introduce an alternative that Roquette site abandon the production of BCD itself and simply purchase it from China.

Toluene: Toluene is classified in category 2 for reproductive toxicity and is a highly flammable liquid (Flam. Liq. 2) with an inherent explosion risk. Furthermore, toluene is on the CoRAP list with the possibility for a more stringent hazard classification. The use of toluene as an alternative is considered by the applicant to give no benefit for the environment or for human health or from an economic point of view, and the quality of the product will decrease.

RAC agrees that this alternative is of no benefit for human health or the environment.

Tetrachloroethylene/Perchloroethylene: PERC is classified in category 2 for carcinogenicity. The use of PERC as an alternative is considered by the applicant to give no benefit for the environment or for human health and to be extremely punishing for the applicant from an economically and technically point of view.

RAC agrees that this alternative is of no benefit for human health or the environment.

Dichloromethane: Dichloromethane is classified in category 2 for carcinogenicity. The use of dichloromethane as an alternative is considered by the applicant to give no benefit for the environment or for human health, and technically and economically dichloromethane is not considered as a feasible alternative to TCE.

RAC agrees that this alternative is of no benefit for human health or the environment.

Cyclohexane: Cyclohexane is not a CMR substance but is a very volatile substance. The performance in the reaction as well as its flammability is considered by the applicant to make cyclohexane unsuitable as an alternative to TCE.

RAC agrees that this alternative is unsuitable as an alternative to TCE due to its volatile properties.

Isopropyl alcohol: Isopropyl alcohol is not a CMR substance, however, the performance in the reaction as well as its flammability is considered by the applicant to make cyclohexane unsuitable as an alternative to TCE.

RAC agrees that this alternative is unsuitable as an alternative to TCE due to its flammability.

Solvent free process – gas chromatography: The efficiency and technical practicability of solvent free processes are considered by the applicant to be unsuitable as alternative to the use of TCE, they consider this alternative as hypothetical.

RAC agrees that the use of a solvent free process – gas chromatography will reduce the risk compared to the use of TCE, however, the efficiency and technical practicability makes the alternative unsuitable as an alternative to TCE.

7.4 Would the available information on alternatives appear to suggest that substitution with alternatives would lead to overall reduction of risk?

☐ YES

☒ NO

☐ NOT APPLICABLE

Justification:

With respect to the substitutes for TCE included in the applicant's non-use scenario (toluene), the available information on alternatives indicate that there will be no reduction in risk achieved by substitution, owing in particular to the hazardous properties of toluene.

7.5 If alternatives are suitable (i.e. technically, economically feasible and lead to overall reduction of risk), are they available?

☐ YES

☐ NO

☒ NOT RELEVANT

Justification:

8. For non-threshold substances, or if adequate control was not demonstrated, have the benefits of continued use been adequately demonstrated to exceed the risks of continued use?

☒ YES

☐ NO

☐ NOT RELEVANT, THRESHOLD SUBSTANCE

Justification:

Values used in SEA for worker exposure to TCE

The estimated statistical number of cancer cases has been calculated by RAC in table 4. This calculation is based on the excess risk for kidney cancer following inhalation and dermal exposure to TCE presented in section 6 and the number of exposed workers provided by the applicant. It reflects the expected number of statistical cancer cases for an exposure over the working life for workers

Table 4: Calculated number of estimated statistical kidney cancer cases from a working life-time exposure of 40 years

Working activity	**Estimated statistical number of kidney cancer cases**
WCS 1 (1)	7.656×10^{-8}
WCS 2 (2)	4.652×10^{-5}
WCS 3 (6)*	5.87×10^{-4}
WCS 4 (2)	6.9×10^{-5}
WCS 5 (1)	2.26^{-6}
Total	7.05×10^{-4}

Benefits of continued use

In the application the switch from TCE to toluene was described as a "non-use" scenario. However, since the applicant also indicated importing BCD from Asia

may replace the lost production, SEAC has requested that the applicant considers also this option as a 'non-use' scenario.
As a result, the applicant identified import of BCD from China as a "non-use" scenario.
The applicant identified several possible socio-economic impacts, if authorisation would not be granted:

Impacts for the applicant:
The applicant would have additional transport costs, an increase in analytical costs (quality control) and additional processing (among others: purification, filtration and concentration) costs, which would amount to a total cost in the range of 1-10 M € for the period of 12 years.

Social impacts:
10 employees would be made redundant.

Risks of continued use
For the calculation of the health impacts of continued use, exposure (workers: dermal and inhalation, general population: inhalation and oral) is quantitatively linked to the health effect of interest. In this case kidney cancer has been identified as the sole source of the excess risks.

RAC's dose-response relationship was used in the applicant's assessment assuming worker exposure of 8 hours per working day over a working life of 40 years.

The applicant arrived at an estimate interval of 272 euros (central value) for the period of 12 years to 1319 euros (worst case scenario) for the period of 12 years which was calculated for the estimated 7.05×10^{-4} statistical kidney cancer cases.

Initially, the applicant did not calculate the health impact via the environment, however, upon request, they provided additional data which resulted in 6.6×10^{-8} statistical kidney cancer cases, with negligible costs (under 1 euro) for the period of 12 years.

Comparison of benefits and risks of continued use
To conclude, the costs of non-authorisation exceed even the upper bound, worst case human health benefits estimates by very significant margin (more than a thousand-fold). **Therefore, SEAC concludes that the benefits of continued use have been adequately demonstrated to outweigh the risk.**

9. Do you propose additional conditions or monitoring arrangements

☒ YES

☐ NO

The applicant must implement regular campaigns of occupational exposure measurements (sampling at least annually) relating to the use/s of TCE described in this application. These monitoring campaigns must be based on relevant standard methodologies or protocols and comprise both personal inhalation exposure sampling and biomonitoring (measurement of the TCE metabolite TCA in urine), be representative of the range of tasks undertaken where exposure to TCE is possible and of the total number of workers that are potentially exposed (i.e. the campaign shall include process and maintenance workers).

The results of the monitoring must be included in any subsequent authorisation review report submitted.

10. Proposed review period:

☐ Normal (7 years)

☒ Long (12 years)

☐ Short (…. _years)

☐ Other:

Justification:

In identifying the review period SEAC took note of the following considerations

- RAC provided no advice on the length of the review period.
- The production of betacyclodextrin (BCD) occurs through an enzymatic process activated by a solvent where the main process improvements and discoveries are made through simple trials and errors and empiric studies.
- The applicant conducted a broad (literature and in-house) search for alternatives from 2003 onward. Certain solvents work best with specific strains of enzymes, and tests showed that with the applicant's enzymes TCE works best.
- The applicant considers that the only solution lies in the discovery of a new strain of enzymes. They have an enormous array of enzymes in their laboratories and they continually research new strains and varieties, besides following the academic developments. In case an appropriate enzyme/solvent system is found a period of 12 years is not unreasonable to fully implement the new process given that, among other issues, a requalification of pharmaceutical products and development of an industrial scale synthesis would have to be undertaken.

SEAC concludes that research and development efforts already made did not lead to the development of an alternative that could be available

within normal review period.

The remaining risks are low and the socio-economic benefits are high (more than ten thousand fold), and there is clear evidence that this balance is not likely to change in the next 12 years.

Taking this into consideration, SEAC recommends a "long" review period of twelve (12) years.

Annex I Worker exposure data: Use at industrial site:
Exposure values applied to estimate the number of kidney cancer cases written in bold text.

WCS n=5	Title and PROC	Route of exposure	Number of measurements or model applied	90th percentile	Mean/ Median	Duration	Frequency	Persons/ shift	PPE/RPE normally used in WCS (see CSR)	APF for applied RPE	Table no. in CSR
1	Storage (PROC 1). TCE is delivered and stored on site in SAFE-TAINER systems of steel barrels of 200 L volume Daily use at site: 0.02 tonnes/day, in total 3 tonnes/year. TCE is used in	Inhalation mg/m3 Dermal mg/kg bw/day	ECETOC TRA v3 ECETOC TRA v3		**0.008** **6.8×10^{-4}** ($240\ cm^2$)	< 1 hour	2 times/year for 3 months	2	PPE (gloves, assumed to reduce exposure by 90 %) no RPE (Outdoor)	-	20

	two campaigns of 3 month/year										
2	Transfer of substance using dedicated facilities (consisting of 3 reactors of 600 litre each) (PROC 8b)	Inhalation mg/m3 Dermal mg/kg bw/day	ECETOC TRA v3 ECETOC TRA v3		**1.916** **0.274** (960 cm^2)	< 1hour	2 times/year for 3 months	2	PPE (gloves, assumed to reduce exposure by 90 %) RPE: yes (Outdoor)	10	21
3	Use in batch processes with opportuni	Inhalation mg/m3	ECETOC TRA v3		15.33	< 1 hour	2 times/year for 3 months	6	PPE (gloves, assumed to reduce exposure by 90 %) no	-	22

	ty for exposure (PROC 4)	Inhalation mg/m3	Personal monitoring (3)		**0.3**				RPE		
			Stationary monitoring (2)		0.17025[1] <0.15139[2]	298 min 303 min					
		Dermal mg/kg bw/day	ECETOC TRA v3		**0.137** (480 cm^2)						
4	Maintenance and cleaning of the equipment (PROC 8a)	Inhalation mg/m3	ECETOC TRA v3		**3.832**	< 2 hour	2 times/year for 3 months	2	PPE (gloves, assumed to reduce exposure by 90 %) RPE: yes (outdoors)	10	23
		Dermal mg/kg	ECETOC TRA v3		**0.274** (960 cm^2)						

[1] Top of reactor
[2] Treatment area TCE

		bw/day									
5[3]	Use as laboratory agent (PROC 15)	Inhalation mg/m3 Dermal mg/kg bw/day	ECETOC TRA v3 ECETOC TRA v3		**0.328** **0.007** (240 cm^2)	< 1 hour	2 times/year for 3 months	2	PPE (gloves, assumed to reduce exposure by 90 %) no RPE	-	24

[3] WCS 5 is not longer relevant, according to the applicant

Measurements with Dräger tubes from inspection tours showed levels of <5 mg/m3 for WCS3/2/3 and <25 mg/m3 for WCS4. These were not applied by the (co-)rapporteurs and are not listed in the annex.