ANALYSIS OF ALTERNATIVES

PUBLIC VERSION

Legal name of applicant: Roquette Frères

Submitted by: Roquette Frères

Substance: *Trichloroethylene (CAS: 79-01-6)*

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

Use number: **1**

CONTENTS

DECLARATION

ROQUETTE

DECLARATION

We, Roquette Frères, request that the information blanked out in the "public versions" of the Socio-Economic Analysis and Analysis of alternatives are not disclosed. We hereby declare that, to the best of our knowledge as of today (August 13, 2014) the information is not publicly available, and in accordance with the due measures of protection that we have implemented, a member of the public should not be able to obtain access to this information without our consent or that of the third party whose commercial interests are at stake.

Lestrem, August 13, 2014

François Creton
regulatory affairs manager

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SOCIETE ANONYME AU CAPITAL DE [illegible] EUROS RCS ARRAS [illegible]

1. SUMMARY

The document below covers the analysis of alternatives for the use of TCE in the production of BCD. The alternative examined in greatest detail is the one used by the largest global manufacturer of BCD even though that company produces in the USA and serves a different market than the applicant. The document concludes there are no alternatives primarily because the technical function of the substance cannot be met and even the least bad alternative has considerable negative economic consequences out of all proportion with the reduction of risk (if any) that is obtained. An additional problem for the applicant is that any change of solvent will have considerable consequences for his downstream users who will be faced with a heavy administrative and financial burden if substitution is mandated. The document concludes with a request for a 12 years authorisation for the continued use of 3T of TCE at the Lestrem site of Roquette Frères.

2. ANALYSIS OF SUBSTANCE FUNCTION

Although the applicant has important sales in other markets, it has highest market share in BCD and HPBCD used in pharmaceutical products due to its very clean manufacturing process and high purity in the final product. In general its Chinese and American (manufacturers) competitors concentrate on the higher volume but lower added value food market for BCD.

2.1. Products manufactured with the use of TCE (trichloroethylene)

Roquette uses TCE in the production of cyclodextrins, which are cyclic oligosaccharides obtained from the degradation of starch by enzymes. The molecules of cyclodextrin are composed by several glucose units and according to their number it is possible to distinguish between several *native* cyclodextrins:

- Alpha-cyclodextrin (6 glucose units)
- Beta-cyclodextrin (7 glucose units)
- Gamma-cyclodextrin (8 glucose units).

Among the 3 types of cyclodextrins, Roquette produces only beta-cyclodextrin. Beta-cyclodextrins (BCDs) are the native cyclodextrins with the highest industrial usage. In order to improve their properties and notably to increase their solubility, the native Beta-cyclodextrins have been chemically modified and the most important ones are:

- HPBCD – hydroxypropyl betacyclodextrin, which is the derivative of cyclodextrin with the ideal profile for pharmaceutical products;
- MBCD –methyl betacyclodextrin.

The applicant produces Kleptose cyclodextrins which are Native Cyclobetadextrin and Hydroxypropylbetacyclodextrin (HPBCD). The final substances have a variety of uses ranging from consumer products, food, cosmetics, home care products, packaging and

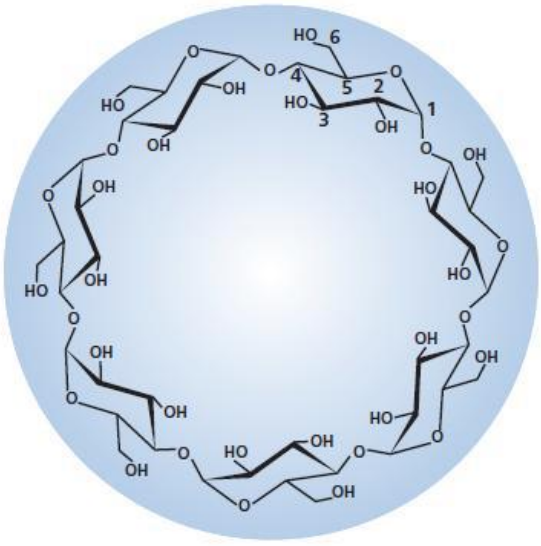


Figure 1 Native Cyclobetadextrin

pharmaceuticals. With nearly one patent being published per day the use of cyclodextrins is increasing all the time. When looking at all possible applications of cyclodextrins, they permit the molecular encapsulation of substances, improve the stability and solubility in aqueous media or reduce the volatility, mask unpleasant odours or taste, stabilize aromas, increase the solubility of active ingredients, avoid incompatibilities between actives in the same formulation, permit the extraction of unwanted compounds (like cholesterol in butter).

2.2. BCD transformation to HPBCD

For Roquette Frères BCD is in itself an important product but equally if not more important is the use the applicant makes of BCD which is the manufacturing of Hydroxypropyl-beta-cyclodextrin (HPBCD). HPBCD is a molecule with higher added value than BCD and Roquette is the leading supplier of this substance to the pharmaceutical industry. HPBCD is the most frequently used cyclodextrin in pharmaceuticals where it is the leading excipient used in patents and new pharmaceutical applications. The unique characteristics of cyclodextrins are useful for the transmission of the active substance to the patient whilst minimizing unpleasant aspects of it as well as optimizing absorption. Many current and most new active substances in pharmaceuticals have low to poor solubility which poses challenges in making the substance available to the patient. The molecule acts like a sort of bin within which one can store active substance to be delivered to the patient.

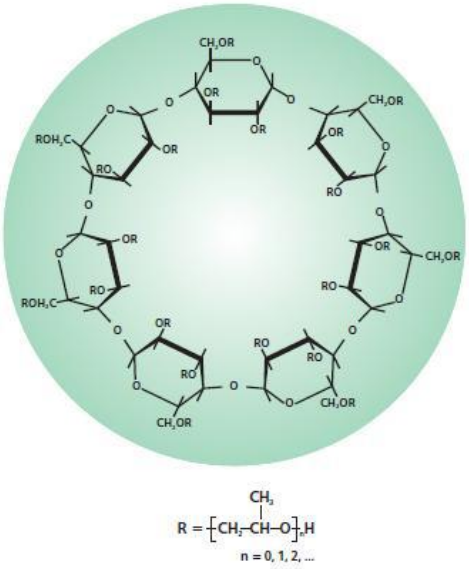


Figure 2 HPBCD

HPBCD are purified polydiverse products resulting from the controlled reaction of propylene oxide and native BCD under base catalysis. Although TCE is not involved in the manufacture of the HPBCD itself, it is nonetheless relevant for the uses in pharmaceutical products as will be outlined below in the section on criteria that alternatives need to meet if they are to acceptable substitutes for TCE.

2.3. Chemical reaction process

The lay person's explanation of the reaction is that the solvent once in contact with the starch molecule and the enzymes causes the starch to form a cyclic molecule with useful properties. The process is catalytic but some losses are observed. Furthermore the solvent eventually acidifies and

needs to be renewed to work efficiently. The process is enzymatic based on original research[1] by – *inter alia* – the applicant in the 1980ies.he addition of the solvent activates the enzymes and improves the reaction that complexates the starch from around 20% at 70°C to 70% or more depending on the solvent used and its compatibility with enzymes The enzymes are produced from strains of bacilli (primarily *bacillus macerans* and *bacillus circulans*) which are the active parts of the biochemical process that creates the BCD. The exact manner in which the enzymes manage this transformation of glucose into a cyclic molecule is not precisely understood but has been observed in empirical studies in Europe and Japan since the mid-seventies to eighties. In common with other enzymatic processes the speed at which the reaction takes place is influenced by several factors and notably the presence of an activator. The TCE performs this function for the process within Roquette Frères.

2.4. Applicant's process for producing BCD

The production of BCD takes place in a rather small section of Roquette Frères's production location at Lestrem, France. The Lestrem site is the largest starch manufacturing location in Europe creating large volumes of products. BCD and HPBCD even more so, are comparatively low volume products ranging rather in the low thousands to barely a few hundred tonnes of product. The process is performed in what is essentially a R&D pilot site location managed from a control room located in proximity to the actual reactor vats. Production is usually performed no more than 6 months per year with the machinery and tools being used for other purposes (such as testing alternatives to TCE) in the intervening time. Normally there is no human intervention in the process after the connection of the TCE safetainer to the system although workers will occasionally be in the vicinity of the vats. The majority of control is performed from within the separate control room. The TCE is stripped from both air and water emissions and reused until it acidifies and a refresher unit is required. The full process can be schematically outlined as follows:

[1] Biosynthesis of Cycloglocosyltransferase and obtention of its enzymatic reaction products. P.J. Siccard, M-H. Saniez.

Figure 3 Reaction flowchart for BCD production

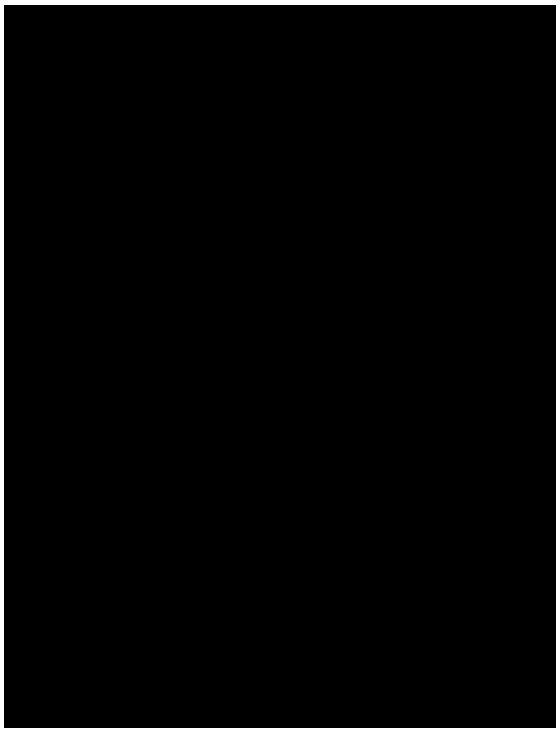


Figure 4 Production native BCD

The BCD itself is purified, crystallised and subsequently made ready for packaging and sales to customers or further transformation as required.

On an aerial picture the Lestrem plant, the site where TCE is manufactured is almost too small to see as it is set right within the larger production units. For reasons that will be made clearer below, the physical place of the reactors is relevant for the choice of alternative. The schematic below depicts it in some more detail:

Figure 5 Snapshot of production area of BCD

3. ANNUAL TONNAGE

The authorisation is requested for the use of 3 Metric Tonnes (MT) of TCE per year, the current usage is just below 2 MT but the applicant sees a growing market for BCD and HPBCD which will involve scaling up the production. Since the technological breakthrough to allow industrial scale production of BCD their unique properties have been predicted[2] to be useful in dozens of new medicines. This prediction has not only been repeated many times since but pharmaceutical companies and their suppliers have seen continual growth in the sales of BCD and HPBCD at medical grade. A recent publication[3] by Dr. Ralph Lipp explained that 80% of new drug discoveries are low soluble and highly permeable which presents challenges for the delivery of the drugs as the

[2] Biosynthesis of Cycloglocosyltransferase and obtention of its enzymatic reaction products. P.J. Siccard, M-H. Saniez.

[3] American Pharmaceutical Review April 30, 2013 The Innovator Pipeline: Bioavailability Challenges and Advanced Oral drug delivery Opportunities.

body would normally excrete them before they become bio-available. The products offered by the applicant respond to this need which is why the application requests authorisation for a larger tonnage than the actual one.

4. IDENTIFICATION OF POSSIBLE ALTERNATIVES

4.1. Main criteria to take into account when examining alternatives

For the purposes of this AoA there are a number of specific considerations that need to be taken into account for establishing the suitability of an alternative to the use of TCE for Roquette. They are:

- 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;
- Required energy input to make the reaction occur c.q. to improve its efficiency;
- Rules on solvent residues for food or pharmaceutical products
- (Non) Flammability of the solvent and consequences for the applicant's installation;

4.1.1 Qualification, authorization or notification of a new BCD and if relevant HPBCD process, fromthe applicant or the applicant's customers Compatibility with enzymatic reaction processes

Enzymatic biochemistry is by and large an empiric exercise where one attempts to find suitable candidates to perform a certain function. In this case that function is the cycling of glucose molecules. This CGTase has been examined through trial and error since decades both with a view to finding the bacteria best suited to create the highest yield but also the ones most resistant to parasitical strains, most prone to have their reaction activated and so forth. These concerns are particularly true when one considers production on an industrial scale. Originally it was even considered that whilst the cyclic molecule created in the laboratory had interesting properties it would never be possible to produce it in sufficient quantities to make it useful in real applications. BCD's have therefore been produced in a variety of ways but many of them are totally impractical for industrial scale production. Finally the choice of activator is related directly to the genus of the bacilli used, the choice for the most sympathetic agent is the subject of extensive tests but – as

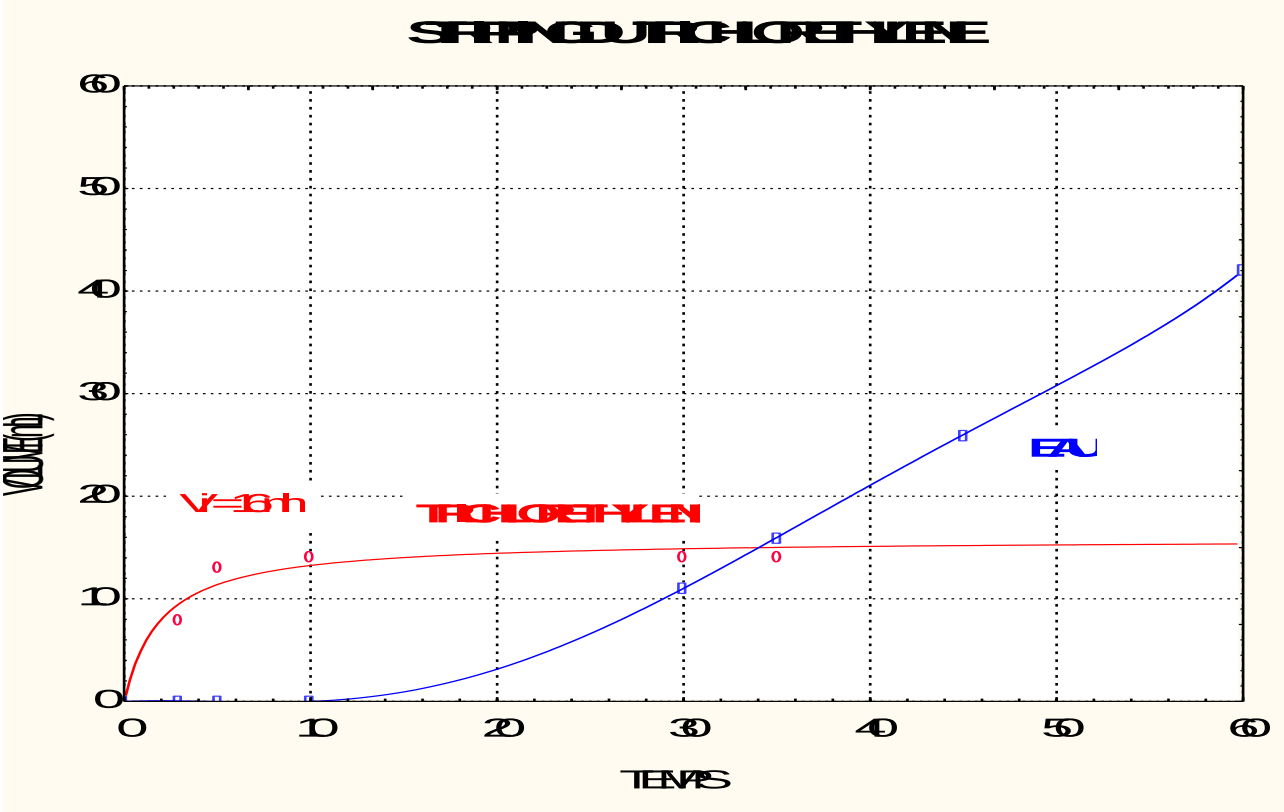
noted above – the actual process is not always understood in every detail. In part this leads to the perhaps somewhat dissatisfying conclusion that for the applicant TCE is best simply because it has been shown in tests to be the most effective agent for the applicant's particular biochemical reaction.

4.1.2 Efficiency of the reaction compared to TCE

TCE manages to activate the enzymes to complexate more than 70% of the sugars in a two hours process. As biochemical reactions variations in solvent, temperature and additional time will show variations but they should preferably arrive within reasonable distance of the applicant's current process. If this efficiency would fall too dramatically, the choice for the applicant would be simple; simply purchase (or manufacture) the BCD's outside of the European Union and focus on its highest margin business the production of HPBCD.

4.1.3 Stripping of the solvent

Although the reaction is catalytic it is necessary to strip the solvent from the final product and recover it for reuse or disposal. For TCE this process has been refined by the applicant so that only minimal losses occur and thanks to volatility the cost and the time of stripping (energy mainly) are very modest and short. This step is non-trivial in the total process and has a major impact on the decision to choose one method or another. Based on in house tests the applicant has derived the following chart describing the recovery of the TCE in the BCD production process:



As can be seen from the chart by 35mn the quasi totality of the TCE has been recovered from the process and can be readied for re-use. Air recovery of TCE in the process is 100% so that almost all the solvent can be reused time and time again. Eventually the solvent does acidify during the process due to the presence of the sugars which means that the solution needs to be sent back to the producer for cleaning and a fresh batch of solvent added to the BCD process. Ideally any alternative should be as easy to strip and suitable for recycling as TCE.

4.1.4 Required energy input

The current reaction process takes place at a constant 70°C – some other solvents require higher temperatures or much longer reaction times at this same temperature. The extension of the current 2hr cycle based on 24/7 production during six months can have appreciable consequences on the cost involved in using an alternative.

4.1.5 Is the solvent permitted?

The use of solvents – particularly in food and pharmaceutical products – is obviously regimented closely by the authorities. It is useless to consider alternatives that are not permitted or recognised under the current guidance or legislation for these products as this is a process of many years with a very uncertain outcome. Furthermore the monograph on BCD was finalised just very recently and is

not due for review for a long while. The applicant sells his product world-wide and is constrained by legislation setting the permitted solvents and their respective levels in dozens of countries. For the purposes of this AoA we propose to take into account:

- FAO/WHO Combined Compendium on Food Additive Specifications ISSN1817-7077, PP. 431-435;
- Directive 2008/84 Food additives – revised to 2010/67 on 21/10/2010 – p. 120
- Codex Alimentarius: General Standard for Food Additives Stan 192-199;
- European Pharmacopoeia 7.0 – p. 583 section 5.4 Residual solvents; version 8.0 pp. 1653-1655
- FCC Monograph PP. 259-261;

All these – as well as further national or international norms and legislation, severely limit the scope of choices for alternatives to the use of TCE. Whilst not inconceivable that this should change in future this is not predictable and cannot be influenced by the applicant.

4.1.6 Flammability

As has been shown above the current installation with which the applicant works is right in the middle of its larger starch production. One of the attractions of the current solvent is that it is not flammable and therefore requires no precautions in this respect. The main known alternative used outside of Europe in more than be irritant, reprotoxic cat.2 or harmful by inhalation, is highly flammable and would require a change to the licenses for the Lestrem site by the French authorities and the physical relocation to another site to comply with ATEX [4] regulations.

4.1.7 Requalification

The products used in pharmaceuticals are subject to extensive authorisation processes of their own. Excipients used in the manufacture of pharmaceuticals are an important part of this chain of authorisation. The authorisation is not only limited to the use of a particular substance with a specific set of known (permitted) residues but even to a specific manufacturer, process and sometimes location. Depending on the nature of the process change a minor or major adaptation of the pharmaceutical's authorisation may be required. Whilst it is hard to guess whether the EMA

[4] 99/92 EC

(European Medicines Agency) would qualify a change of solvent as minor or major – there are arguments for both – at a minimum several months of work are required for the applicant's customers and at worst many years including expensive clinical trials to be performed. Finally for one disease[5] HPBCD is examined as active substance and any changes would set back the treatment of this orphan disease practically to square one.

4.2. List of possible alternatives

The applicant believes that there is only a limited number of methods that allow the enzymatic synthesis of BCD:

1) Solvent free production through gas chromatography;
2) Solvent based processes
    a. Toluene (CAS. 108-88-3);
    b. Perchloroethylene (CAS. 127-18-4);
    c. Dichloromethane (CAS. 75-09-2);
    d. Cyclohexane (CAS. 110-82-7);
    e. Isopropanol (CAS. 67-63-0).

Finally an alternative that would involve the applicant abandoning production of BCD itself and simply purchasing it from China for example, should be considered.

Globally the use of any other alternative than toluene is marginal in terms of production (low yield), not permitted by food regulation and toluene is – therefore – the alternative the applicant has examined most closely.

4.3. Description of efforts made to identify possible alternatives

4.3.1. Research and development

[5] European Medicines Agency Public Summary of opinion on orphan designation for Niemann-Pick type C disease. 7th May 2013. In the US the treatment has already received orphan drug status. This status releases public funds for the development and marketing of drugs for which there is no commercial market available – generally when the amount of patients are below 5 in 10,000. For Niemann-Pick the number is 0.1 in 10,000 or just about 5,000 persons in the whole of Europe.

The original invention of the BCD production method dates back to the 1980ies which concluded that TCE was the most efficient solvent for the production. It took a considerable amount of time for uses to be discovered for BCD and the applicant did not start to consider industrial production until the late nineties. When this process was underway in the early 2000's the applicant became aware that TCE would be reclassified and that therefore substitution was desirable even if there was no risk in manufacturing or in the final product. A large scale project was funded to examine the alternatives and to decide on whether substitution or better control of the current process was desirable.

In 2003 an extensive set of tests was performed within the Roquette installation. The process needs to be operated in the actual production plant and cannot be tested just in theory. The production of BCD takes place within what the applicant would call their small laboratory but this also serves as the actual production facility when batches are manufactured. The plant is operating roughly 6 months a year leaving the other half of the year to test alternatives or do other things with equipment as desired. Based on literature research the examined alternatives were:

1) Toluene – at 50°C and 70°C;
2) Perchloroethylene – at 50°C and 70°C;
3) Dichloromethane – at 50°C[6].

The test method was to add 187.5 grams (0,165 mol) of BCD with 1500g of demineralised water. At 70°C the BCD will be completely solved into the water, the pH is modified from 4.5 to 6. Then over a 15mn process 0.354 mol of solvent is added and the mixture is left at the desired temperature (50° or 70 °C) for three hours. Over the time of the reaction samples are taken after decantation over 5 minutes. Through the desiccation of these samples one can determine the efficiency of the reaction by determining the amount of BCD that has not reacted. In 2008 the results of the 2003 research were re-examined in some detail notably deepening the comparison between the reduction of risk of TCE to toluene. Both times the establishment of a toluene using setup was examined right down to draft plant redesign plans and costings. Otherwise attention was of course also given to the other elements described in the introductory part to this section. In 2013 the analysis was further refined by examining which solvent was permitted in which country for every application.

[6] As Dichloromethane has a boiling point 70°C it did not make sense to try it out at the higher temperature. The insertion valve in the process is not inserted in the mixture so in gas form no reaction would occur.

The results of all these researches are reflected in the AOA below but it should be no surprise that the conclusion remained that TCE whilst requiring caution to handle was the best option available to the applicant by a large margin.

4.3.2. Data searches

The production of BCD is a specialist activity in which a limited number of companies are involved. There is not much literature and the biggest source of data searches was performed in the examination of what the competitors of the applicant use in their processes.

The main competitor of the applicant is [redacted] which the applicant believes has a global market share of approximately [redacted]%. [redacted]s production is based in [redacted], their primary clients are food companies and the solvent used is Toluene. There are also [redacted] [redacted]companies[7] with market shares over [redacted]% globally some of whom produce HPBCD as well and some that do not. As far as the applicant is aware these companies sometimes use TCE and sometimes toluene. There are a further set of companies[8] including [redacted] which market shares around [redacted]% globally where again some use toluene and some TCE. Finally there are a further group of [redacted], [redacted], [redacted] and [redacted] companies with market shares of less than [redacted]% of these it is known that some ([redacted] only) use a gas chromatography solvent free method.
What sets aside the applicant from the majority of their competitors is its focus on pharmaceutical companies and the delivery of high grade very pure and virtually residue free HPBCD. The actual number of competitors is therefore likely to be smaller than the list above leads one to presuppose.

As referenced in the specific sections there is some academic literature regarding the industrial production that is acknowledged as authoritative, the conclusions of these articles are taken into account in the overview below:

1) *"Biosynthesis of Cycloglocosyltransferase and obtention of its enzymatic reaction products."* P.J. Sicard, M-H. Saniez privately published by Roquette Frères 1982;

[7] [redacted].

[8] [redacted]

2) *"Effects of organic solvents on enzymatic production of cyclodextrins from unliquified corn starch in an attrition bioreactor",* Biotechnology and bioengineering, vol. 39 no. 10,Yun-Song Lee, Hak-Sum Kim 25/4/1992,
3) *"Cyclodextrins and their Industrial Uses",* D. Duchêne 1987
4) ORSAN-MERCIAN Corp. EP 481.903 - 1992

4.3.3. Consultations

The applicant did not hold any consultations on the subject because there seemed to be little to gain from such an exercise. The only likely respondents would be competitors with whom information could not be shared for competition reasons whereas the applicant's engineers routinely follow the academic research into BCDs.

5. SUITABILITY AND AVAILABILITY OF POSSIBLE ALTERNATIVES

a) ALTERNATIVE 1: Gas chromatography – solvent free

5.1. Substance ID and properties: not applicable

There is a process using UV to synthesize the BCD from the starch. This was possibly even the first method used to develop the molecule in the seventies in Japan.

5.2. Technical feasibility

The problem with this method was recognised at its very inception[9], whilst technically feasible it is inconceivable to have an industrial scale production through this process. The efficiency of the reaction is very low with 20%[10] being the upper bracket of the process' best result. The applicant is aware of a few places where this technology is used for laboratory purposes but there is no industrial scale production. The applicant is also unaware of any method that would allow the

[9] Biosynthesis of Cycloglocosyltransferase and obtention of its enzymatic reaction products. P.J. Siccard, M-H. Saniez.

[10] Ref. *Inter alia:* Biotechnology and bioengineering, vol. 39 no. 10,Yun-Song Lee, Hak-Sum Kim 25/4/1992, Cyclodextrins and their Industrial Uses, D. Duchêne 1987 and ORSAN-MERCIAN Corp. EP 481.903 - 1992

scaling up of this technology to within anywhere the volumes of production that can be achieved with solvent based methods. In effect this is only suitable for the tiniest volumes (below 1 MT).

5.3. Economic feasibility

Apart from the need to design a completely new installation and the concomitant cost of that exercise the efficiency of the reaction is far too low for it to be competitive with the other methods that are available.

5.4. Reduction of overall risk due to transition to the alternative

The method reduces the risk compared to the use of TCE.

5.5. Availability

The applicant would contend that whilst this technology exists it is not available on a scale suitable for the purposes of the applicant

5.6. Conclusion on suitability and availability for Alternative 1: solvent free

The efficiency and technical practicability of the solvent free processes make them unsuitable as alternatives to the use of TCE. It is even fair to say that this option is only hypothetical.

b) ALTERNATIVE 2: Toluene (CAS. 108-88-3);

5.7. Substance ID and properties: Toluene (CAS. 108-88-3);

Toluene is the most commonly used solvent for the production of BCD globally and has been the subject of repeated studies by the applicant. The solvent is also permitted[11] as a residue for both

[11] The fact the solvent is permitted as a residue about 800 times more than TCE does not necessarily make it more desirable for the customer who may well prefer the much lower residue of TCE than the higher one in toluene.

food and pharmaceutical applications in concentrations much higher than for TCE in pharmaceutical applications. Some basic characteristics are set out in the table below (TCE included for reference):

Characteristic	TCE	Toluene
Stability	Poor (-)	Good (+)
Boiling point	87°C	110°C
Flashpoint	Non flammable	4°C
Limit explosiveness	N/A	1.2-7.1%
Toxicity	CMR 1B (H350)	CMR2, H361d cat2,H225 cat2
	H315 cat2, H317cat1b, H319 cat2, H341 cat2, H336 cat.3, H412 cat3	H315 cat 2,H304 cat1,H373 cat2, H336 cat.3
Solubility in water	73°C-7%	84°C-13%
Pictograms	Exclamation mark and open chest	Exclamation mark, Flame, open chest

5.8. Technical feasibility

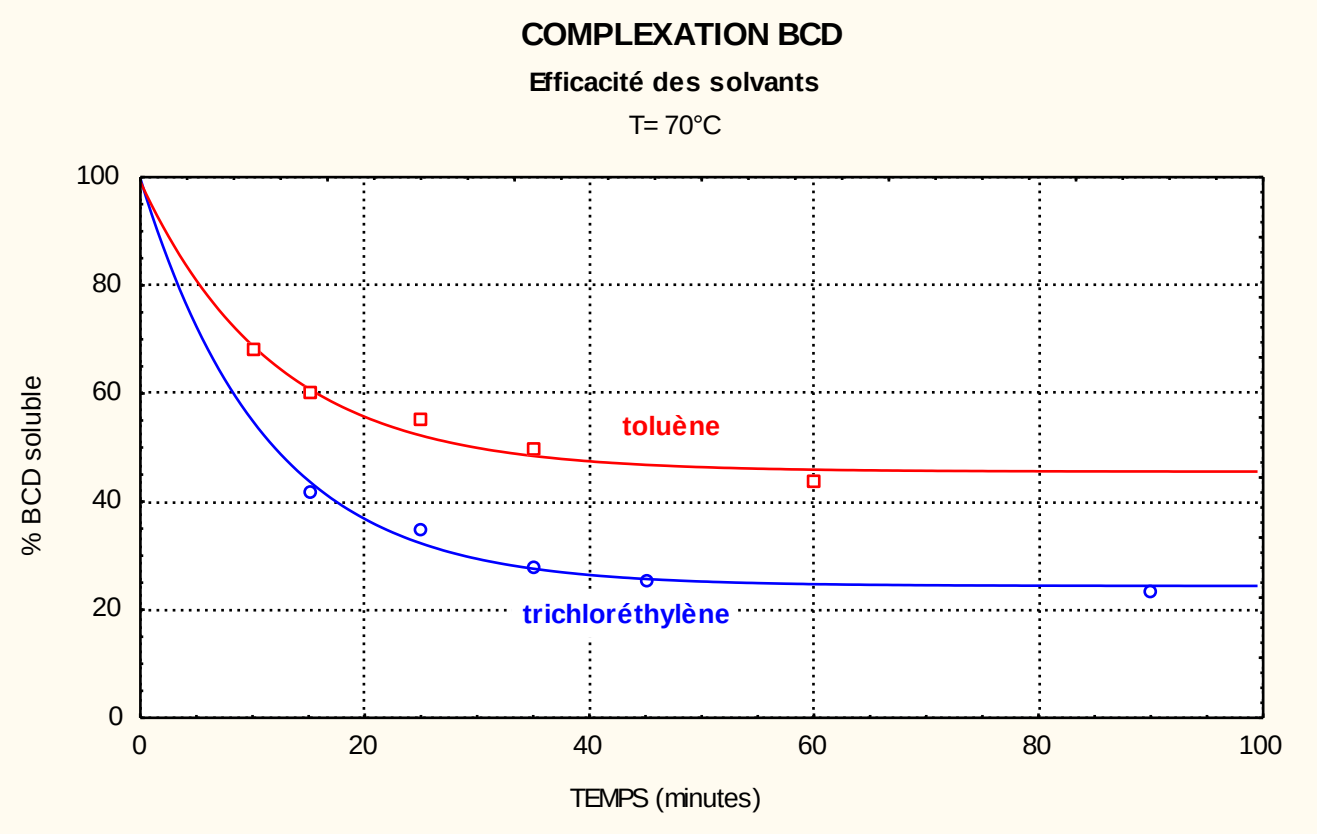
The reason why toluene fails the technical feasibility test rests upon three main criteria:

- Efficiency of the reaction;
- Poorer stripping ability of the toluene compared to TCE;
- Installation and environmental licensing changes required of the Lestrem site.

Additionally other arguments covered in the economic section are also (in practice) of a more or less technical nature: the current installation is unsuitable and impossible to transform to the usage of toluene, the change of solvent has major requalification implications for the pharmaceutical customers, to increase the efficiency of the toluene reaction additional heat and much extended reaction time are required which also pose technological challenges.

5.8.1 Efficiency of the reaction

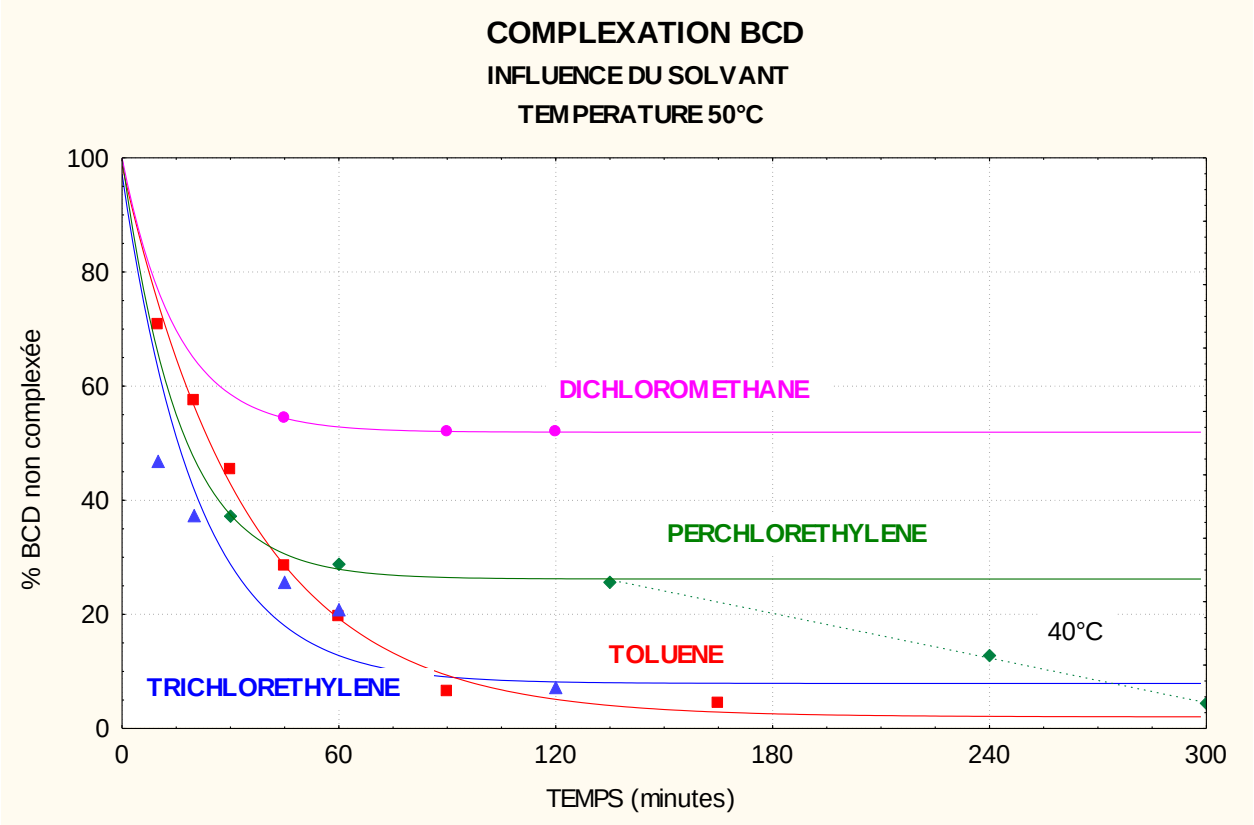
The toluene enzymatic reaction to create the BCD is the most closely studied[12] and reported on technology. These publications estimate the efficiency of the reaction at >50%. The applicant has several times performed in house studies of the process using toluene and found consistent results despite attempted variations of the process and method. The chart shows the result at the current



process temperature of 70°C over a period of up to 100 minutes. Toluene achieves roughly 55% complexation of the starch into BCDs whilst TCE achieves over 75%. This difference in efficiency means that TCE is a third more efficient than toluene based on the study performed by the applicant. It should also be noted that the curve of TCE is much sharper than the one for toluene so that after 20mn TCE has almost achieved its maximum potential whilst toluene is not near its total efficiency at all.

The same process was repeated (chart in this case for several solvents) to examine the efficiency of the reaction at 50°C.

[12] Ref. *Inter alia:* Biotechnology and bioengineering, vol. 39 no. 10,Yun-Song Lee, Hak-Sum Kim 25/4/1992, Cyclodextrins and their Industrial Uses, D. Duchêne 1987 and ORSAN-MERCIAN Corp. EP 481.903 - 1992



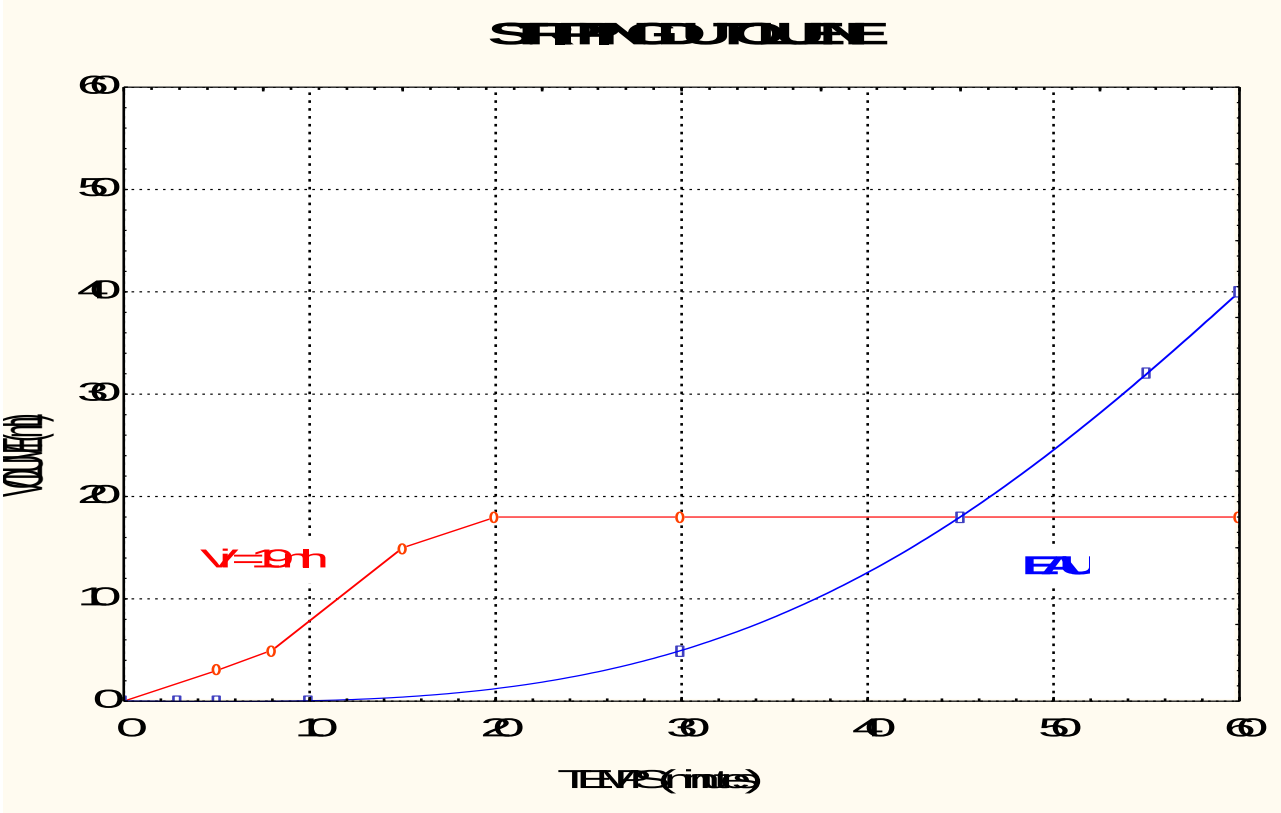
Once again it will be noted that TCE is almost at full efficiency by 60 minutes whilst toluene eventually surpasses it in efficiency but only after another 40mn or so. The incremental gain is also too small to be really meaningful until almost 180 minutes has passed. It is obviously technically much more attractive to stop the reaction after 40 minutes at 70°C than to have to wait 180 minutes at 50°C.

These measurements are based on real life tests by the applicant that are not equivalent to a full academic analysis of the subject. Nevertheless the reactions obtained are generally more favourable (for both TCE and Toluene) than what has been reported in the cited academic literature. It will be obvious that there is a large gap between the efficiency of toluene as a process solvent compared to TCE. The applicant therefore concludes that already on this basis the toluene solvent is not a viable alternative to TCE.

5.8.2 Stripping of the solvent

The removal of the solvent used as catalyst for the reaction is an essential part of the process. Amongst the positive aspects of TCE is the fact that it is relatively easy to strip from the process

(see 4.3.1). The applicant has tested the ability to strip the toluene from the process. The following chart shows the result of this process:



Compared to the TCE stripping outlined in 4.3.1 it will be noted that it takes about 10mn more before the toluene is stripped from the process. Once again this is a non-negligible technical drawback to the use of toluene as compared to the current use of TCE. This slows down the production process and causes additional cost as well.

5.8.3 Installation and licensing changes

Technically one of the biggest issues that prevents the applicant from using toluene are the required changes to the installation and the concomitant environmental licensing and permits changes that would be required. Due to its flammability toluene requires the conformity of the installation to ATEX – this means that the current location and reactor vats cannot be used because they are too close to other installations and do not have the ATEX required perimeter of protection. Whilst there is sufficient room on the Lestrem site to set up a new set of reactors this is equivalent to making a Greenfield investment whereby the current installation is abandoned.

Another important aspect is that the Lestrem site – despite its enormous size – processes relatively benign substances and does not have a permit for handling more than 10 MT of flammable liquids on the current location. Currently the site has 9 MT of Ethyl Acetate required for other processes on

site. The addition of toluene would inevitably make the site exceed the limits of its current permits. Although the construction of a new toluene using reactor is therefore technically feasible, the consequences for the rest of the installation covering several hundred hectares are substantial. Furthermore changes to an environmental permit such as that of the Lestrem site is a process of many years subject to public consultation. With the village of Lestrem near to the plant site it is not inconceivable that a permit to handle explosive substances in higher volumes takes time and would not be forthcoming or if it would be permitted that the conditions would be extremely onerous.

From the perspective of the applicant the use of toluene is therefore highly undesirable and incompatible with its current installation and permits or the market demands. For this reason as well toluene is not a suitable substitute for the applicant.

5.9. Economic feasibility

Economically there are four aspects that play a role when assessing toluene as a potential substitute:

a) Cost of building an ATEX compliant process area on the Lestrem site;
b) Efficiency of reaction and stripping of toluene compared to TCE;
c) Lengthening of the time of the process compared to TCE;
d) Other costs related to the changeover to toluene.

5.9.1 ATEX compliant process area

As has been outlined above the use of toluene requires an ATEX compliant installation. Without regard to the secondary effects of having an ATEX installation on the current site, the applicant calculated the cost to build a new process in 2003 arriving at a cost in excess of [redacted] M €. As the current process site is set firmly inside the larger starch process area of Lestrem there is no opportunity to use toluene there. Given that the risks are well controlled in the current site the investment seems a waste of money for little gain.

5.9.2 Efficiency of reaction and stripping

As has been demonstrated above the reaction with toluene is at least a third less efficient than TCE at $70°C$ the current process temperature. Whereas at the lower temperature toluene eventually is more efficient than TCE but this takes up to three times longer than if TCE is used at the higher temperature. Without making detailed calculations it will be obvious that the lower efficiency or longer operations account for a considerable cost.

5.9.3 Lengthening of the reaction period

Even if one supposes it takes only twice as long when using toluene it would require the installation to be run 12 months per year 24/7 to achieve the same production. The added labour cost is easily > 1 M €/y as 9 workers are involved full time. Furthermore energy for heating the reaction is also required. A doubling of the cost of operation without any benefit, this effectively makes the use of toluene not economically viable.

In addition to this it takes about 1/3 longer to strip the toluene from the process as well. Once again this is a materially negative aspect of the use of toluene that argues against its use.

5.9.4 Other costs

As has been stated above the use of toluene would materially change the nature of the Lestrem site as regards its environmental license. Whilst theoretically possible to apply for a change it is quite unlikely that the permit would be easily granted given the close location of the Lestrem village and the serious consequences that flammable substances could have in case of an industrial accident. The work, study, planning for the review of the environmental license will take many years and will quite possibly cost millions of euros whilst the actual surface taken up with producing BCD is just a fraction of the total Lestrem site. It is therefore disproportionate considering the modest gains in health, safety and environment to consider.

Another consideration is that a switch to toluene will have immediate effect for pharmaceutical clients. The residue of toluene would not currently be declared on their medicine authorisations and would therefore require a review of their dossier. Because residues occasionally have beneficial or negative side effects on the drug used, it is possible that in some, all or a few of the cases new clinical trials will be required. Even for a minor notification of a process change a cost of €100,000 per medicine is not unusual, with currently many dozens of products using HPBCD this cost will quickly add up. The applicant surmises that customers would seek to switch to a non EU based supplier (from China for example) to substitute with HPBCD that conforms to the existing process instead.

5.10. Reduction of overall risk due to transition to the alternative

The applicant refers to the table in the first section regarding toluene. Whilst arguably not an improvement overall it is true that toluene is currently classified as slightly less dangerous than TCE. However the applicant has received notice from the French government that its status is under review as regards the OELs as well as being re-examined for the purposes of REACH[13]. The general expectation is that toluene will come out of the review process with a higher classification than the current one. There is also ample evidence from other sources that point to likely sharpening of the controls over solvents such as toluene. The applicant is therefore of the opinion that the transition to toluene does not present any (material) reduction of risk compared to the use of TCE. The better recovery of TCE and the lower OELs in themselves show that toluene is more dangerous than TCE. Finally as an explosive substance industrial accidents cannot be excluded and these would not occur with an inflammable solvent like TCE. The applicant feels that this in itself negates any theoretical risk reduction offered by toluene.

5.11. Availability

Toluene is plentifully available.

5.12. Conclusion on suitability and availability for Alternative 2: toluene

The applicant has repeatedly (2003, 2008, 2013) examined the viability of switching production to toluene and come to the same conclusion every time, there is no benefit either from an environment or health point of view nor from an economic perspective to make this change. The likely result would be an increase in cost, lower quality final product and a loss of market for the applicant all made on the basis of a considerable upfront investment.

The question remains why the main competitor of Roquette Frères persists in the use of toluene in the United States or in China. The applicant is convinced that this is due to the different nature of the production process at competitors which also serves different purposes than just producing BCD. As mentioned before the reaction is enzymatic and other manufacturer is sure to have own strains of bacilli grown for this process. It is conceivable that these are more sympathetic to Toluene

[13] https://www.anses.fr/fr/content/lanses-publie-ses-recommandations-en-vue-de-r%C3%A9duire-lexposition-%C3%A0-cinq-substances

but there is no known evidence for this that the applicant is aware of. Neither has the applicant ever been able to successfully create a strain of enzymes that display these properties. Furthermore others 'main market is in food additives where the applicant has a more modest place. Instead the applicant focussed on very high quality and added value production for pharmaceutical or other sensitive applications. Switching to toluene would negate this competitive advantage for the applicant whilst in fact increasing the residue of solvent in the final product. With the upcoming review of toluene's classification this may cause further problems.

c) ALTERNATIVE 3: Perchloroethylene (CAS 127-18-4)

5.13. Substance ID and properties: Perchloroethylene (CAS 127-18-4)

As a sister substance to TCE, it seemed logical to examine the possibility of using the variant Perchloroethylene (a.k.a. tetrachloroethylene) instead of TCE.

Characteristic	TCE	Perchloroethylene
Stability	Poor (-)	Poor (-)
Boiling point	87°C	121°C
Flashpoint	Non flammable	Non flammable
Limit explosiveness	N/A	N/A
Toxicity	CMR 1B (H350) H315 cat2, H317cat1b, H319 cat2, H341 cat2, H336 cat.3, H412 cat3	CMR2 cat A R40, R51/53,
Solubility in water	73°C-7%	20°C-15%
Pictograms	Exclamation mark and open chest	Exclamation mark, Dead fish

5.14. Technical feasibility

In the same manner as for toluene – though less often – the feasibility of using Perchloroethylene has been examined by the applicant. The main attraction of the substance is that it is non-flammable and therefore – with minor changes – usable in the current set-up of the applicant. The results of the comparative test in the efficiency of the reaction were – however – extremely disappointing.

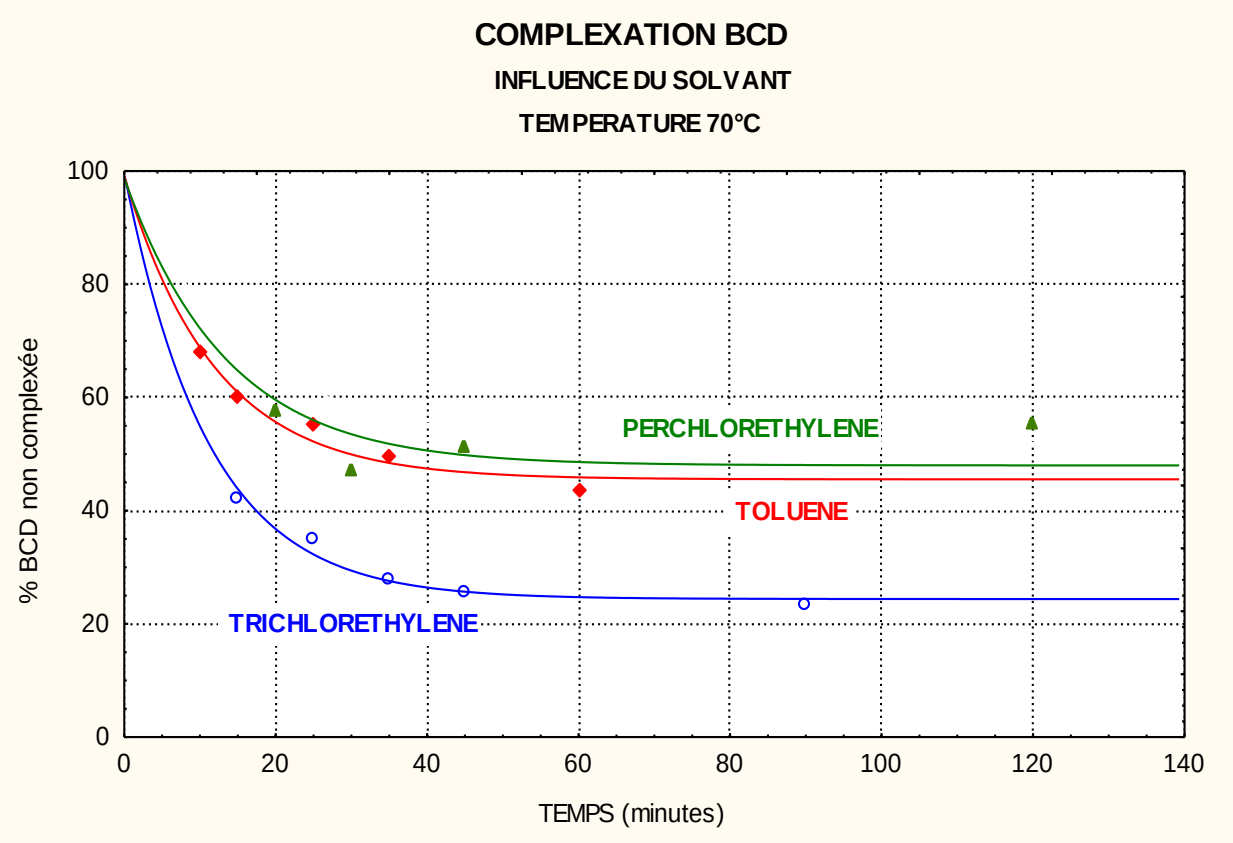


Figure 6 Complexation of BCD with PerCE at 70 C

The situation if the lower temperature of 50°C is used is much worse:

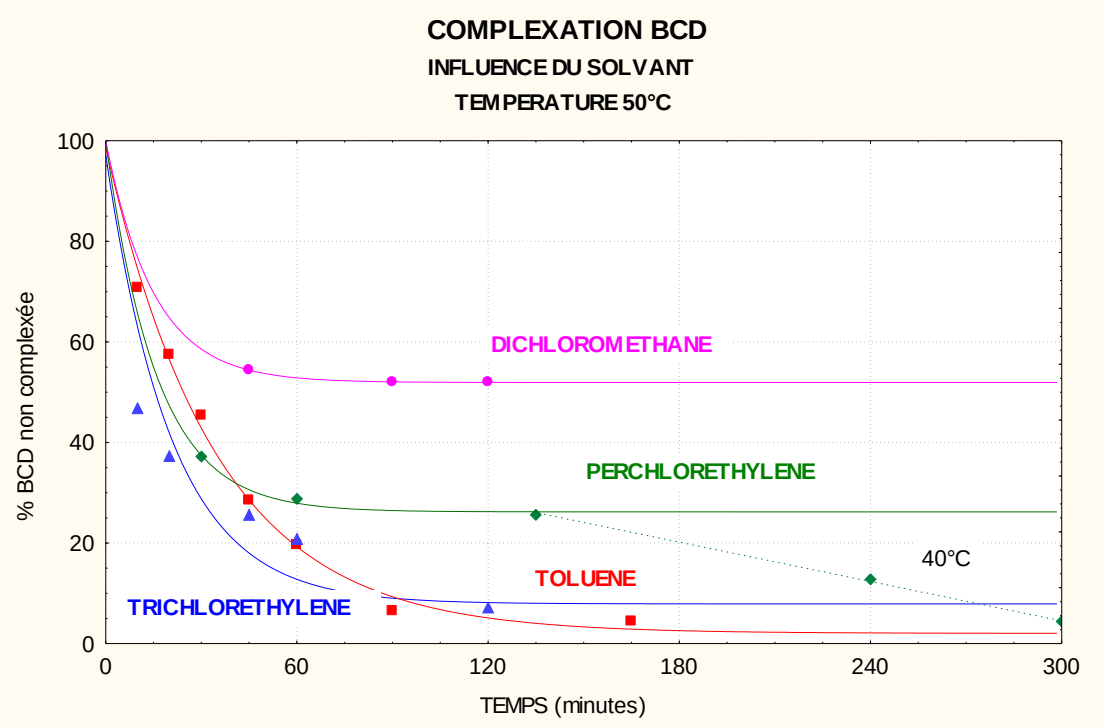


Figure 7 Complexation of BCD with PerCE at 50 C

In both cases the performance of PCE is simply too far away from TCE to be deemed an alternative in a technical sense. The reaction with TCE is 50% more efficient and it seems extremely unlikely that process refinements could bridge this gap or even get close. As regards the stripping the applicant has not made specific research but the higher solubility of PCE may be problematic and lengthen the process.

5.15. Economic feasibility

The transition to PCE has several severe economic impacts for the applicant:

- Reaction efficiency falls by 50% - meaning that the installation must be run 24/7 the year around to create as much BCD. The cost in labour alone exceeds 1 M€/y without any other benefit;
- PCE is not a permitted residue in the pharmaceutical excipient market where the applicant has his strongest position. This means that production of the highly valuable HPBCD would need to be stopped an unacceptable consequence with severe financial losses.
- PCE is not permitted residue in BCD food additive regulation

- considerations above alone make a dissuasive case for the applicant to chose PCE.

5.16. Reduction of overall risk due to transition to the alternative

The status of PCE as a cat 2 CMR means that the advantage from a health perspective is rather limited. Furthermore the applicant understands that PCE may well find itself on the authorisation list within the next 5 years so that a transition would not bring any benefit from that perspective either. Lastly PCE is more persistent and less bio-degradable than TCE in the atmosphere making a choice for PCE less attractive. The applicant therefore considers that there is no reduction of risk associated with the choice for this alternative.

5.17. Availability

PCE is available in sufficient quantities.

5.18. Conclusion on suitability and availability for Alternative 3: Perchloroethylene

The technical and economic visibility of this alternative are extremely punishing for the applicant whereas there seems little if any gain from a health and safety or environment perspective in the choice for this alternative. Therefore the applicant concluded that PCE cannot be considered an alternative to TCE for the purposes of this application.

d) ALTERNATIVE 4: Dichloromethane (CAS 75-09-2)

5.19. Substance ID and properties: Dichloromethane (CAS 75-09-2)

Literature indicates that it is possible to synthesise BCD with the help of dichloromethane.

Characteristic	TCE	Dichloromethane
Stability	Poor (-)	Poor (-)
Boiling point	87°C	40°C
Flashpoint	Non flammable	Very flammable
Limit explosiveness	N/A	N/A

Toxicity	CMR 1B (H350) H315 cat2, H317cat1b, H319 cat2, H341 cat2, H336 cat.3, H412 cat3	CMR2 cat B H315, H319, H335, H336, H351, H373
Solubility in water	73°C-7%	60°C-5%
Pictograms	Exclamation mark and open chest	Exclamation mark, open chest

5.20. Technical feasibility

In the same manner as for toluene – though less often – the feasibility of using dichloromethane has been examined by the applicant. The study was only made at 50°C because the insertion nozzle is over the solution rather than inside it and with a boiling point of 40°C the higher temperature meant that the substance did not mix into the solution. The results found by the applicant are consistent with the results reported in literature research.

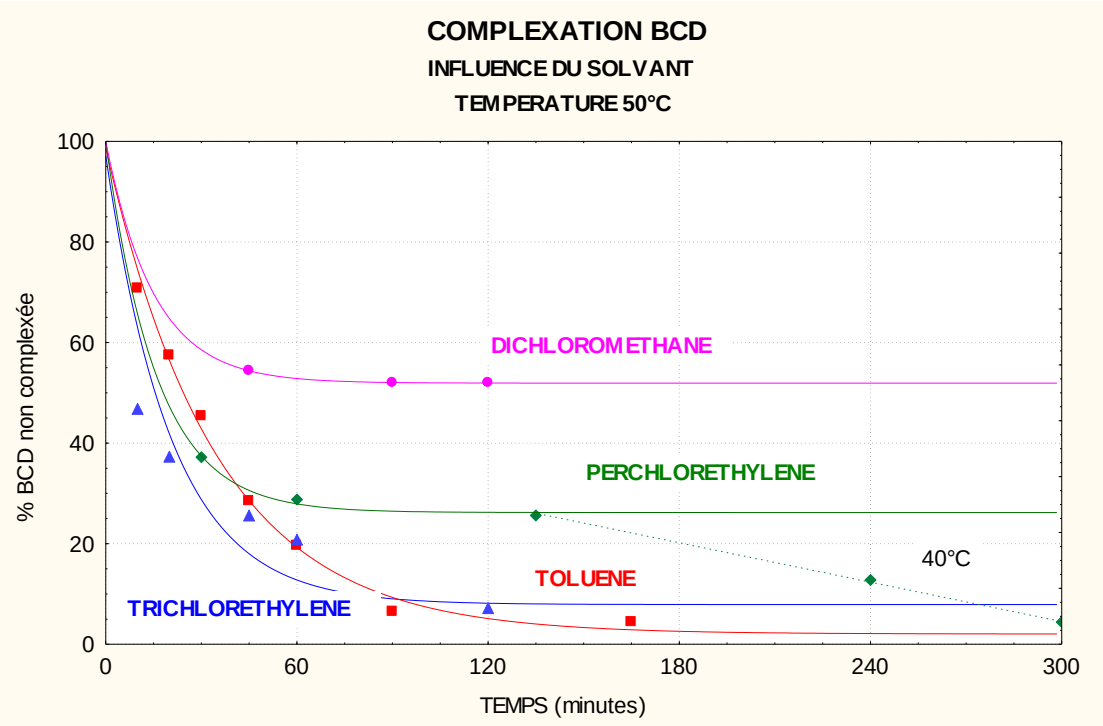


Figure 8 Complexation of BCD with Dichloromethane at 50 C

The performance of Dichloromethane is even worse than that of PCE and toluene for this reason alone it cannot be deemed a feasible alternative to TCE.

5.21. Economic feasibility

The transition to PCE has several severe economic impacts for the applicant:

- Reaction efficiency falls by 80% which means a separate installation committed to just manufacturing the BCD would need to be built because the current equipment would not be sufficient. Furthermore as a flammable substance the same issues would arise as with toluene but with an even worse performance;
- Dichloromethane is a permitted residue in the pharmaceutical market but there are no medicine authorisations known to the applicant for the excipient market where the applicant has his strongest position. This means that production of the highly valuable HPBCD would need to be stopped an unacceptable consequence with severe financial losses.
- Dichloromethane is not permitted residue in BCD food additive regulation

The costs and poorer performance are so blatant that no further research was done into the substance.

5.22. Reduction of overall risk due to transition to the alternative

Dichloromethane is generally reckoned to be the least toxic of the chlorohydrocarbons, however it is an irritant and not without dangers. Fatalities have been reported due to its volatile nature and long term exposure has been linked to cancer. Overall the reduction in risk appears very marginal and hardly worth the effort of substitution.

5.23. Availability

Dichloromethane is available in sufficient quantities.

5.24. Conclusion on suitability and availability for Alternative 4: Dichloromethane

The performance in the reaction as well as its flammability make dichloromethane unsuitable as a substitute for TCE.

e) ALTERNATIVE 5: Cyclohexane (CAS 110-82-7)

5.25. Substance ID and properties: Cyclohexane (CAS 110-82-7)

Literature indicates that it is possible to synthesise BCD with the help of cyclohexane.

Characteristic	TCE	Cyclohexane
Stability	Poor (-)	Stable (+)
Boiling point	87°C	81°C
Flashpoint	Non flammable	Extemely flammable (-20°C flashpoint)
Limit explosiveness	N/A	1.3-8.4%
Toxicity	CMR 1B (H350) H315 cat2, H317cat1b, H319 cat2, H341 cat2, H336 cat.3, H412 cat3	CMR2 cat B H315, H319, H335, H336, H351, H373
Solubility in water	73°C-7%	69°C-9%
Pictograms	Exclamation mark and open chest	Exclamation mark, Fire, Dead fish

5.26. Technical feasibility

Literature consulted by the applicant indicate that cyclohexane can have a yield of ca. 50% in BCD in an enzymatic reaction. This is considerably less than TCE making it unattractive. The main drawback however is the extreme flammability and very low flash point of the substance. This requires a modification of the installation to ATEX norms. Even taking into account such safeguards the applicant feels that the substance would be unsafe to use in a hot reaction like the BCD complexation.

5.27. Economic feasibility

The economic feasibility is at best equivalent to that of toluene due to the important changes required to the installation. Furthermore the issues of residues in both food and pharmaceuticals would be unresolved making the choice of cyclohexane a very poor economic solution for the applicant.

5.28. Reduction of overall risk due to transition to the alternative

Whilst not a CMR, cyclohexane is so volatile that its use would engender a substantial increase in risk for the applicant's installation. The applicant therefore considers that there is no relevant reduction in risk.

5.29. Availability

Cyclohexane is available in sufficient quantities.

5.30. Conclusion on suitability and availability for Alternative 5: Cyclohexane

The performance in the reaction as well as its flammability make cyclohexane unsuitable as a substitute for TCE.

f) ALTERNATIVE 6: Isopropyl alcohol (CAS 67-63-0)

5.31. Substance ID and properties: Isopropyl alcohol (CAS 67-63-0)

Literature indicates that it is possible to synthesise BCD with the help of Isopropyl alcohol (aka Isopropanol).

Characteristic	TCE	Isopropyl alchol
Stability	Poor (-)	Stable (+)
Boiling point	87°C	83°C

Flashpoint	Non flammable	Extremely flammable (13°C flashpoint)
Limit explosiveness	N/A	2-12.7%
Toxicity	CMR 1B (H350) H315 cat2, H317cat1b, H319 cat2, H341 cat2, H336 cat.3, H412 cat3	H225 H319 H336
Solubility in water	73°C-7%	Miscible
Pictograms	Exclamation mark and open chest	Exclamation mark, Fire,

5.32. Technical feasibility

Literature consulted by the applicant indicate that ispropanol can have a yield of ca. 30% in BCD in an enzymatic reaction. This is considerably less than TCE making it unattractive. There is also the drawback that it is the extreme flammable. This requires a modification of the installation to ATEX norms. Finally the boiling point is so low that it would be hard to create an industrial scale installation that could handle the hot process required of the enzymatic reaction. The applicant was unable to directly test this substance but based on the literature and physical chemical properties of the substance it was deemed unsuitable as an alternative.

5.33. Economic feasibility

The economic feasibility has not been examined in detail but would be equivalent to the objections raised for Toluene and the other flammable solvents. Furthermore there is the question of the residues in the final product which are unresolved and would prevent marketing of the final product.

5.34. Reduction of overall risk due to transition to the alternative

Apart from its flammability the substance does offer a substantial reduction of risk compared to TCE.

5.35. Availability

Isopropanol is available in sufficient quantities.

5.36. Conclusion on suitability and availability for Alternative 6: Isopropanol

The performance in the reaction as well as its flammability make isopropanol unsuitable as a substitute for TCE.

6. OVERALL CONCLUSIONS ON SUITABILITY AND AVAILABILITY OF POSSIBLE ALTERNATIVES FOR USE 1

The applicant has performed both in house and literature research examining all possible alternatives to the use of TCE. The conclusion is that the least bad of the alternatives would be toluene but this substance presents little or no risk reduction benefits, has additional hard to quantify risks related to its flammability that would impose excessive costs on the applicant and finally has important effects for the downstream users of the applicant. All other potential alternatives perform even worse than toluene. Considering the closed process in the use of TCE and the severe process, technical and economic difficulties that would fall on the applicant in case of substitution without real corresponding gain in risk reduction, it must be concluded there is an absence of viable alternatives.

The applicant is also of the opinion that it is extremely unlikely other solvents would be found that could perform the function of TCE. Since the late nineties there have been no further successful tests found in literature or in the applicants own research for other solvents. Most of the likely candidates are either chlorinated solvents which present similar risk characteristics to TCE or flammable hydrocarbons. As the least dangerous of these hydrocarbons – dichloromethane – has been tested the applicant concludes that none of that family of alternatives would be suitable. Since

the invention of the synthesis process for BCD around 1970 in total 5 possible solvents have been found but none have been found since 2000. It therefore would be reasonable for the authorisation to be granted for the longest period of 12 years because this reflects the cycle of scientific research results. It should be underlined that research remains ongoing as the future use of BCD and its derivates is likely to see exponential growth and there would be a high premium for anyone inventing a better process than the current one. Roquette Frères would benefit directly if such a solution could be found and therefore have a commercial incentive to keep researching as well as the moral commitment to reduce the use of SVHC's wherever possible. Such a reduction is also part of the normal environmental licensing and occupational exposure checks and processes implemented by the company throughout its global organisation.

ANNEX I – JUSTIFICATIONS FOR CONFIDENTIALITY CLAIMS

Blanked out item reference	Page Number	Justifications for confidentiality	
Figure 3 Figure 4 Figure 5 4.3.2 Investment Cost	p.9 p.9 p. 10 p.17 p.24	1. Declaration	These data on costs, customers, formulations per country, production volumes, consumption, sales, publically available and are claimed confidential in line with Article 119 of REACH.
		2. Commercial interest	These data are known only to Roquette who have measures in place to ensure they are not publicly available. These data are known only within Roquette and the company would be significantly negatively impacted if they were to be available to other market players, competitors and stakeholders as Roquette derives a significant commercial value by maintaining these data as confidential. Details of customers and the assumed formulations by country are also of clear value to the competition. Making these data public would cause commercial harm to Roquette France and to the Roquette Group if they were to become known outside of Roquette.
		3. Potential Harm	Dissemination of these data will cause severe harm to the commercial interests of Roquette. Dissemination of these confidential business information data would contravene current competition law (as defined under Articles 101 and 102 of the Treaty on the Functioning of the European Union) and would be contrary to the stated intention of DG Competition to preserve business secrets (see point 5 in the table below)[14]. Information on customers is of considerable value to the competition who could use these data and – due to the uncertainty in the market place regarding the question of whether authorisation will be granted or not – work in a more targeted fashion to recruit Roquette's customers to their substance offering with supply chain certainty being a significant commercial motivation. .
		4. Limitation to validity of claim	The claim for confidentiality for the data covered by the justifications detailed in this table will remain valid indefinitely.
		5. Business Secrets	These data constitute business secrets as defined by DG Competition[15] as they include ´financial information relating to an undertaking's know-how, methods of assessing costs, production secrets and processes, supply sources, quantities produced and sold, market shares, customer and distributor lists, marketing plans, cost and price structure and sales strategy"

[14] ´***Business secrets*** *merit a very special protection. They are confidential information about an undertaking's business activity';* DG Competition: "Annex: Business secrets and other confidential business information"

[15] See DG Competition's Annex on Business Secrets (2012): Article I.4.

http://ec.europa.eu/competition/antitrust/business_secrets_en.pdf